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Hemodynamic and Neurohumoral Changes after Abdominal Aortic Constriction in Rats

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ABSTRACT

Cardiac after-load, neurohumoral reaction and the secondary cardiac hypertrophy were studied in six groups of Sprague-Dawley (SD) rats with abdominal aortic constriction. We found that abdominal aortic constriction above the renal arteries decreased the heart rate and cardiac output, and increased the pulse pressure. These abnormalities would return to normal after constriction ended. Captopril, propranolol and prazosin could reduce the increase of pulse pressure but still had decreased in cardiac output of rats with abdominal constriction. Aortic constriction also increased the aortic impedance and cardiac load but decreased aortic compliance. These changes could also be lessened by captopril, propranolol and prazosin. We have confirmed that aortic constriction can induce secondary cardiac hypertrophy, but the pathogenesis might be due to multiple factors.

Key Words: aortic constriction, cardiac hypertrophy, hemodynamic, renin, sympatho-adrenergic system

I. Introduction

Long-term work-load increment on a ventricle causes cardiac hypertrophy. The increase of pressure or volume work-load on the ventricle induces the release of catecholamines and hormones (Yagi *et al.*, 1968; Whitlow and Katholi, 1983; Gelman *et al.*, 1990; Symbas *et al.*, 1983; Normann *et al.*, 1983). The initiative factors and maintainance of the process of cardiac hypertrophy remains controversial (Cooper *et al.*, 1985; Morgan and Baker, 1991; Kromer and Riegger, 1985) .

An increase of aortic pressure has been reported to contribute to an increase of aortic impedance, and a decrease of aortic compliance and cardiac hyperfunction associated with neurohumoral responses (Yagi *et al.*,1968; Gelman *et al.*, 1990; Morgan and Baker, 1991; Kromer and Riegger, 1985; Salgado and Krieger, 1986; Salgado and Salgado, 1989; Baker *et al.*, 1990; Sadoshima and Izumo, 1993). Such remarkable hemodynamic changes after aortic constriction may cause secondary cardiac hypertrophy (Salgado and Salgado, 1989; Lompre *et al.*, 1984). However, the initiative factors causing cardiac adaptive hypertrophy require further clarification. The feasibility of reversing the process of cardiac hypertrophy after removal of the causal factor must also be examined.

In this study, we analyzed hemodynamic changes and sympathetic activities in rats during aortic constriction and after constricted ended to evaluate its role in cardiac adaptive hypertrophy. An understanding of the pathogenesis of cardiac adaptive hypertrophy may provide valuable information for the prevention of this particular cardiac hypertrophy and therapeutic intervention in certain situations in which there is an increase of afterload, such as with coarctation of the aorta.

II. Materials and Methods

1. General Preparation

Male Sprague-Dawley (SD) rats which were 10 weeks old and weighed about 300 gm each were used. The rats were anesthetized with intraperitoneal (IP) injection of sodium pentobarital (40 mg/kg). A tracheostomy was performed to provide artificial ventilation with a tidal volume of 3-5 ml and a respiratory rate of 50-70 breaths/min. The abdominal wall was opened, and the abdominal aorta was isolated in the pre-renal area. We used 3-0 nylon stitch to constrict the aortic lumen to a fixed size using a 0.67-0.86 mm probe around it above the point at which the renal arteries branched as previously described (Haddad *et al.*, 1996; Everett *et al.*, 1994). One shot of benzathine penicillin G (10,000 units/kg IP) was administered to prevent wound infection. Aortic constriction was relieved using the same pre-medication.

The rats were divided into six groups. (1) Group A: thirteen rats received a sham operation as control; (2) Group B: ten rats were subjected to abdominal aortic constriction for six weeks without other medication; (3) Group C: fourteen rats were subjected abdominal aortic constriction for two weeks, but constriction was relieved for the next four weeks; (4) Group D: ten rats subjected to abdominal aortic constriction for six weeks; following the operation, the rats also received IP injections of captopril, 10 mg/kg/day, for six weeks; (5) Group E: twelve rats received for six weeks IP injections of propranolol, 4 mg/kg/day, since the same day of abdominal aortic constriction; (6) Group F: eleven rats received six weeks of IP injections of prazosin, 0.1 mg/kg/day, following the first day of abdominal aortic constriction. Six weeks later, studies were performed on all the experimental rats to measure: (1) the steady hemodynamic components, including the aortic peak systolic, mean, end-diastolic and pulse pressures (*APs*, *APm*, *APd*, *PP*), heart rate (*HR*), stroke volume (*SV*), cardiac output (*CO*), and peripheral resistance (*Rp*); (2) the pulsatile hemodynamic components, including the first modulus of input impedance (*Z1*), characteristic input impedance (*Zc*), the compliance of the peak systolic, mean, end-diastolic pressures (*Cs*, *Cm*, *Cd*), the first zero crossing frequency of the impedance phase angle (*fo*), the external steady, oscillatory, and total power (*Ws*, *Wo*, *Wt*), the magnitude of the backward and forward components of the pressure wave (*Pb*, *Pf*); and (3) the concentrations of the catecholamines in the myocardium of the left ventricle (Liu *et al.*, 1986; Cheng *et al.*, 1993).

2. Hemodynamic Changes

After the rats had been anesthetized, the femoral artery was cannulated to record the femoral arterial pressure, and the femoral vein was cannulated to administer supplemental anesthetics and fluid. The chest was opened, and an electromagnetic flow probe (Carolina Medical Electronics Inc., Chapel Hill, NC, U.S.A., Model 100 series, internal circumference 7 mm) was then placed around the ascending aorta to measure the velocity of blood flow in the aorta. A Millar catheter (Millar Instruments Co., Houston, TX, U.S.A., Model SPR-407, Size 2F) with one high-fidelity pressure sensor was used to measure the aortic pressure. To minimize the baseline drift, the catheter was soaked in saline at room temperature for at least one hour before insertion. The Millar catheter was inserted via the isolated right carotid artery into the ascending aorta until the catheter tip reached a position just distal to the flow probe. The distal end of the carotid artery was ligated. The aortic pressure, flow waves and electrocardiogram (ECG) were continuously monitored via a polygraph recorder (Gould, Cleveland, OH, U.S.A., Model 2800S) and also recorded on a tape recorder (TEAC, Chiyoda-Ku, Tokyo, Japan, Model MR-30) at a recording speed of 4.8 cm/sec for off-line analysis. Finally, a lead II ECG was recorded with a Gould ECG/Biotech amplifier.

3. Calculations and Data Analysis

The pressures and flow signals were digitized at 4 ms intervals using a 12-bit analog-to-digital converter (Microstar Laboratories Inc., Bellevue, WA, U.S.A., Model DAP 1200/4) interfaced with a personal computer. Signals (six consecutive beats at steady state) were selected on the basis of the following criteria: (1) recorded beats with optimal flow velocity profile; (2) beats with a RR interval less than 5% different from the average value of all the recorded beats during a stable state; (3) stable and regular respiration without fighting against the respirator. Zero flow was assumed to be the value of the flow in the middle to late diastole. The largest modulus of this portion of the flow was considered to be the noise level. The descending aorta was cannulated and connected to a resistor. From the digitized flow velocity signal, we determined the time-averaged flow velocity for at least thirty separate beats. This mean velocity was converted to volume flow by multiplying it by the flow probe's cross-sectional area. The appropriate calibration factor for each rat was then determined by matching the cardiac output with the mean output calculated from the digitized flow signal. The flowmeter (Carolina Medical Electronics Inc., Model 501D) had a frequency response that was decreased by 3 dB at 100 Hz. The phase lag was almost linear with the frequency (1.2 degrees/Hz). Appropriate corrections were applied at each impedance harmonic to take the phase delay into account. All the hemodynamic parameters were calculated beat by beat. The average hemodynamic data of four beats was obtained for an individual data point.

The impedance modulus was the ratio of the aortic pressure harmonic to the flow harmonic. The flow phase was subtracted from the pressure phase at each harmonic to obtain the impedance phase angle. Any flow harmonic with a modulus < 1.5 times the noise level was not used for impedance calculation. The characteristic impedance was the average of the impedance moduli in a frequency range of 15-45 Hz with coefficients of variation < 10%. The first zero-crossing of the impedance phase angle was evaluated using linear interpolation method based on the data. The systolic, diastolic and mean aortic pressure, the heart rate, stroke volume and systemic vascular resistance were also determined for each beat. The arterial compliance at pressure *P* (systolic, diastolic or mean) was obtained using the equation given by Liu *et al.* (1986) for an exponential pressure-volume relationship (Salgado and Krieger, 1986). The total external power (*Wt*), consisting of both the pressure and kinetic terms for the left ventricle, was calculated. We also evaluated the oscillatory power (*Wo*), the steady power (*Ws*), and the ratio of oscillatory to total power (*Wo/Wt*) as an index for the efficiency with which pulsatile energy was converted into forward flow. The measured pressure and flow waves included their forward and backward components. The magnitudes of the pulse pressure of the forward (*Pf*) and backward (*Pb*) components along with the ratio of the backward to forward magnitude were used to characterize the wave reflection properties.

The procedures for measurement of the aortic pressure and flow and for arterial impedance analysis were essentially similar to those described previously (Salgado and Krieger, 1986). The procedures caused a fall in arterial pressure as reported in previous studies (Salgado and Krieger, 1986). The extent to which the surgical procedures and blood pressure reduction affected the hemodynamic data remains unclear. We discarded the data in which the fall in arterial pressure exceeded 20 mmHg after thoracotomy and flow-probe placement.

4. Catecholamines Assays

The rats were then sacrificed, and their hearts were isolated. The atria , appendages and right ventricular free wall were cut off. The left ventricle and ventricular septum were preserved and weighed. The ratio of left ventricle weight to body weight was calculated (LVW/BW). From the left ventricular free wall, a sample of around 100mg was taken and homogenized (500 rpm, 2 min) in 1 c.c. ice-cold 0.1 M hydrochloric acid containing 10^{-7} M ascorbic acid. 6000 g of the homogenate was centrifuged at 4 ºC for 15 min to remove the precipitated protein and cell debris, and then filtered through a Millipore 0.22 μm filter (Ultra free-MC, Millipore, Bedford, MA, U.S.A.). 5-μ1 of filtrate was directly injected into a high-performance liquid chromatography system with dual electrode electrochemical detection (HPLC-DUED) (Cheng *et al.*, 1993).

The concentrations of norepinephrine (NE) and epinephrine (EPI) were calculated by determining each peak-area ratio relative to the standard Isopropylene Tryptamine (IPT) in both anodic and cathodic chromatograms.

5. Statistical Analysis

The results are expressed as Mean ± SE. Different groups were compared by using one factor ANOVA and the Fisher's protected least significant difference (PLSD) test. Differences were considered to be significant at a value of $P < 0.05$.

III. Results

1. Hemodynamics of Steady Component

Tables 1 and 2 summarize the hemodynamic data of the rats in each group. Although the systolic aortic pressure increased after aortic constriction in every group of rats, it had statistical significance only in the rats in Group F ($P < 0.05$). The increment in the pulse pressure was significant in Group B, which had the longest duration of aortic constriction. The pulse pressure was 47 ± 5 mmHg after 6 weeks of aortic constriction and was significantly different from normal control. The increased pulse pressure returned to normal after aortic constriction ended or after administration of vasodilators (Tables 1 and 2). The aortic and pulse pressure were nearly equal in Groups A, C, E and F. In Group F, there was significantly higher systolic, diastolic and mean pressure, about 10 mmHg ($P < 0.05$) more than that of control group, but the pulse pressure did not change significantly. The heart rate changed significantly except in Group C. It increased in Groups D and F and decreased in Groups B and E. *CO* significantly changed in Groups B, C, D, E and F. It dropped significantly in Group B because of the slowing heart rate. After aortic constriction ended, *CO* rebounded even more than the normal control because of the increase of the stroke volume. The drop in *CO* in the rats in Groups D, E and F, might have been due to the effects of the slowing heart rate caused by the vasodilators. However, *CO* and peripheral resistance (*Rp*) were not significantly different between Groups D, E and F. This indicated almost similar effects of these three vasodilators on cardiac output and peripheral resistance.

2. Hemodynamics of Pulsatile Component

Z1 increased significantly in Groups B, D, E and F. It is easily to understand the increase of *Z1* in the rats after aortic constriction. Captopril, propranolol and prazosin significantly affected the increment of *Z1* and *Zc* after aortic constriction (Tables 3 and 4). *Zc* displayed a significant

Table 1. Results of Aortic Pressure, Heart Rate, Cardiac Output and Peripheral Resistance in Different Rats with Abdominal Aortic Constriction and Release

	Aortic pressure (mmHg)			*PP*	*HR*	*SV*	*CO*	$Rp \times 10^3$
	Aps	*Apm*	*Apd*	mmHg	Beats/min	ml	ml/min	dyne·s·cm^{-5}
Group A (*n*=13)	121 ± 4	105 ± 4	90 ± 4	31 ± 4	383 ± 6	0.22 ± 0.01	85.8 ± 1.6	101 ± 11
Group B (*n*=10)	124 ± 5	100 ± 4	77 ± 3	47 ± 5	335 ± 5	0.22 ± 0.01	76.2 ± 1.7	106 ± 10
Group C (*n*=14)	122 ± 4	103 ± 5	86 ± 4	36 ± 4	373 ± 8	0.26 ± 0.01	92.2 ± 2.0	90 ± 10
Statistical Significance (P ¡ 0.05)				A vs B B vs A, C	A vs B B vs A, C C vs B	A vs C	A vs B, C B vs A, C C vs A, B	B vs C

Note: Values expressing as mean ± SD

Abbreviations: *Aps* = aortic pressure at peak systole; *Apm* = mean aortic pressure; *Apd* = aortic pressure at end diastole; *PP* = pulse pressure; *HR* = heart rate; *SV* = stroke volume; *CO* = cardiac output; *Rp* = peripheral resistance; Group A = control group; Group B = banding for 6 weeks; Group C = banding for 2 weeks and then released for 4 weeks

Table 2. Results of Aortic Pressure, Heart Rate, Cardiac Output and Peripheral Resistance in Different Rats with Vasodilator Effects

	Aortic pressure (mmHg)			*PP*	*HR*	*SV*	*CO*	$Rp \times 10^3$
	Aps	*Apm*	*Apd*	mmHg	Beats/min	ml	ml/min	dyne·s·cm^{-5}
Group A (*n* = 13)	121 ± 4	105 ± 4	90 ± 4	31 ± 4	383 ± 6	0.22 ± 0.01	85.8 ± 1.6	101 ± 11
Group D (*n* = 10)	135 ± 4	110 ± 5	89 ± 4	36 ± 5	425 ± 6	0.19 ± 0.01	79.2 ± 1.6	116 ± 10
Group E (*n* = 12)	125 ± 4	109 ± 4	94 ± 4	31 ± 4	359 ± 5	0.22 ± 0.01	77.8 ± 1.8	115 ± 10
Group F (*n* = 11)	138 ± 5	121 ± 5	108 ± 5	30 ± 4	358 ± 6	0.22 ± 0.01	79.6 ± 1.9	119 ± 10
Statistical Significance (P ¡ 0.05)	A vs F	A vs F	A vs F E vs F		A vs D, E, F D vs A, E, F E vs A, D F vs A, D	A vs D D vs A, E E vs D	A vs D, E, F	A vs D, E, F

Note: Values expressing as mean ± SD

Abbreviations: *Aps* = aortic pressure at peak systole; *Apm* = mean aortic pressure; *Apd* = aortic pressure at end-diastole; *PP* = pulse pressure; *HR* = heart rate; *SV* = stroke volume; *CO* = cardiac output; *Rp* = peripheral resistance; Group A = control group; Group D = banding and captopril for 6 weeks; Group E = banding and propranolol for 6 weeks; Group F = banding and prazosin for 6 weeks

increase in Group B. The decrease of aortic compliance due to aortic constriction recovered after constriction ended and could be prevented by captopril, propranolol or prazosin administration (Fig.1, Tables 3 and 4). The wave velocity indicated by *fo* increased significantly in Group B, and the increment of *fo* was reduced in rats after constriction ended with administration of captopril, propranolol or prazosin although still abnormal higher than that of the control group. The external power increased significantly after aortic constriction with the changes in aortic impedance and compliance. The relief of constriction and vasodilators administration markedly influenced the elevation of *Wo* and *Wo/Wt*. However, the reduction of *Wo* to a normal value was noted only in Group E. The magnitude of the pressure wave was significantly elevated after aortic constriction. The elevation of *Pb* and *Pf* could not be depressed to normal by relieving aortic constriction or administering vasodilators, except for Pb in Group F and *Pf* in Group E. Furthermore, the *Pb/Pf* ratio increased significantly in Groups D, E and F (Tables 3 and 4).

3. Ventricular Hypertrophy and Cardiac Catecholamines Concentration

Tables 5 and 6 show the severity of ventricular hypertrophy and the amount of neurohumoral content in the myocardium. The LVW/BW ratio increased significantly in the experimental rats, including Groups B, C, D, E and F, as compared with the control group. The ventricular hypertrophic ratio (LVW/BW) was significantly reduced after aortic constriction ended. However, it was unaffected by vasodilator administration and was not different in the rats which received captopril, propranolol or prazosin administration. Left ventricular NE was depleted after aor-

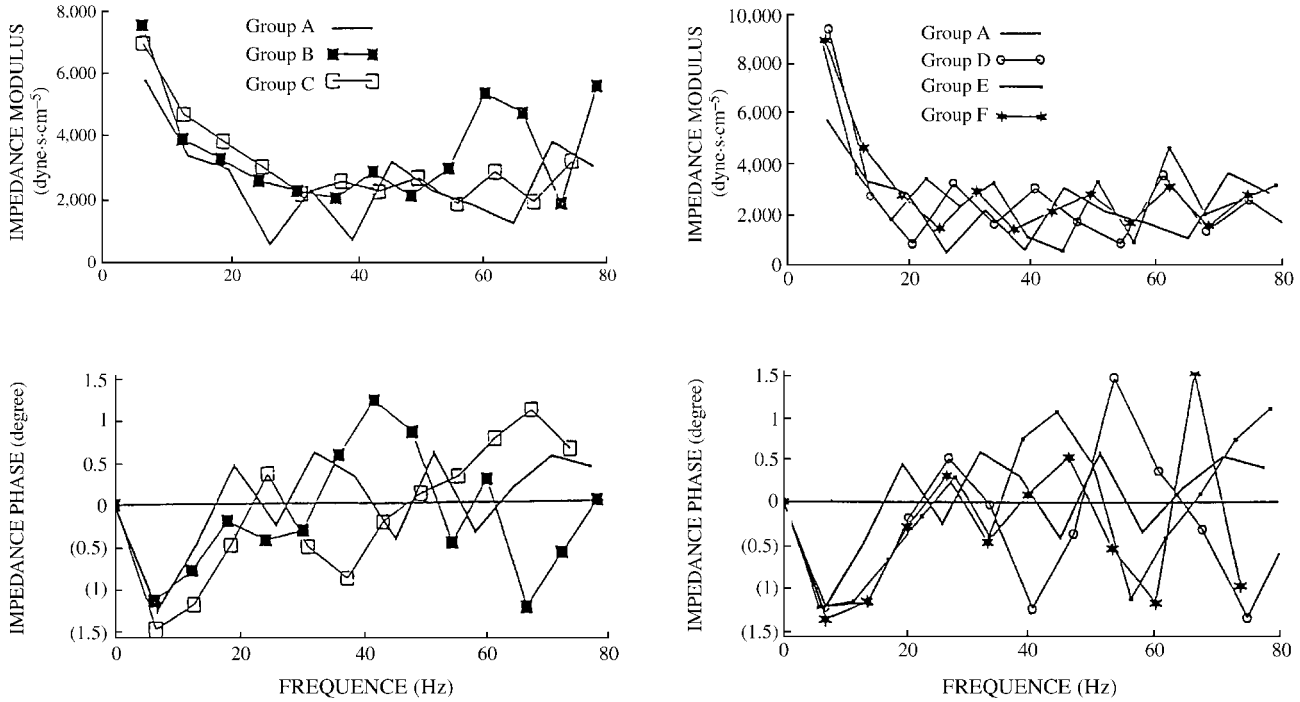

Fig. 1. The first modulus of impact impedance and impedance phase of the average of four beats at the steady state of the rats in control and studied groups.

Table 3. Results of Aortic Impedance, Ventricular Work and Wave Reflected in Different Rats after Abdominal Aortic Constriction and Release

	Zl	*Zc*	*Cd*	*Cm*	*Cs*	*fo*	*Wo*	*Ws*	*Wo/Wt*	*Pb*	*Pf*	*Pb/Pf*
	dyne·s·cm^{-5}			μl/mmHg		Hz	mW		%	mmHg		%
Group A: (n = 13)	6218 ± 312	1946 ± 119	3.67 ± 0.38	3.12 ± 0.36	2.56 ± 0.25	14.9 ± 1.5	1.02 ± 0.09	19.2 ± 2.0	5.1 ± 0.7	6.8 ± 0.5	10.1 ± 1.0	71 ± 6
Group B: (n = 10)	11150 ± 43	3121 ± 193	2.39 ± 0.26	1.86 ± 0.14	2.13 ± 0.21	23.4 ± 2.1	1.61 ± 0.17	16.6 ± 1.3	8.8 ± 1.3	11.2 ± 1.1	16.5 ± 2.2	72 ± 7
Group C: (n = 14)	6914 ± 289	2053 ± 137	3.40 ± 0.36	2.82 ± 0.30	3.10 ± 0.29	19.9 ± 1.3	1.34 ± 0.23	20.6 ± 2.0	6.5 ± 1.1	8.4 ± 0.8	12.0 ± 2.0	72 ± 9
Statistical Significance (P ¡ 0.05)	A vs B B vs A, C C vs B	A vs B B vs A, C C vs B	A vs B B vs A, C C vs B	A vs B B vs A, C C vs B	A vs B B vs A, C C vs B	A vs B, C B vs A, C C vs A, B	A vs B, C B vs A, C C vs A, B	B vs C	A vs B, C B vs A, C C vs A, B	A vs B, C B vs A, C C vs A, B	A vs B, C B vs A, C C vs A, B	

Note: Values are mean ± SD

Abbreviations: *Zl*: first modulus of input impedance
Zc: characteristic input impedance
Cd: compliance at end-diastole
Cm: compliance at mean pressure
Cs: compliance at peak systole
fo: first zero crossing frequency of impedance
Wo: oscillatory power
Ws: steady power
Wt: total external power
Pb: backward component of pressure wave
Pf: forward component of pressure wave
Group A: control group
Group B: banding for 6 weeks
Group C: banding for 2 weeks and released for 4 weeks

tic constriction ended, but NE depletion stopped and was preserved in rats after constriction ended. The total NE content decreased in all the studied groups, but decreased less in Groups C and F. This indicated that the depletion of NE might have been prevented by relieving aortic constriction or administering prazosin. EPI were also dropped significantly in the myocardium after aortic constriction ended, inspite of the early relief of constriction. However, the administration of propranolol and captopril could prevent the depletion of EPI in the myocardium.

IV. Discussion

Cardiac hypertrophy generally results from structural

Table 4. Results of Aortic Impedance, Ventricular Work and Wave Reflected in Different Rats with Vasodilator Effects

	Zl	*Zc*	*Cd*	*Cm*	*Cs*	*fo*	*Wo*	*Ws*	*Wo/Wt*	*Pb*	*Pf*	*Pb/Pf*
	dyne·s·cm^{-5}			μl/mmHg		Hz	mW		%	mmHg		%
Group A: (n = 13)	6218±312	1946±119	3.67±0.38	3.12±0.36	2.56±0.25	14.9±1.5	1.02±0.09	19.2±2.0	5.1±0.7	6.8±0.5	10.1±1.0	71±6
Group D (n = 10)	8351±335	1912±125	2.89±0.21	2.48±0.18	2.59±0.22	20.1±1.4	1.30±0.20	20.2±2.0	6.3±1.0	9.2±1.0	11.5±1.9	80±9
Group E: (n = 12)	8253±381	1884±124	3.36±0.28	2.82±0.20	3.02±0.26	21.7±1.3	1.16±0.11	18.6±1.7	6.0±0.9	8.5±0.9	10.3±1	83±9
Group F: (n = 11)	8391±394	1846±127	3.00±0.25	2.56±0.19	2.67±0.21	20.9±1.9	1.22±0.12	21.6±2.0	5.3±0.7	7.8±0.7	9.0±1.1	86±5
Statistical Significance (P ¡ 0.05)	A vs D, E, F		A vs D, E, F D vs A, E E vs A, D F vs A	A vs D, F D vs A, E E vs D F vs A	A vs E, F D vs E E vs D	A vs D, E, F	A vs D, F	E vs F	A vs D, E D vs A, F E vs A F vs A, D	A vs D, E D vs A, F E vs A F vs D	A vs D, F D vs A, E, F E vs D F vs A, D	A vs D, E, F

Notes: Values are mean ± SD

Abbreviations: *Zl*: first modulus of input impedance
Zc: characteristic input impedance
Cd: compliance at end-diastole
Cm: compliance at mean pressure
Cs: compliance at peak systole
fo: first zero crossing frequency of impedance
Wo: oscillatory power
Ws: steady power
Wt: total external power
Pb: backward component of pressure wave
Pf: forward component of pressure wave
Group A: control group
Group D: banding and captopril for 6 weeks
Group E: banding and propranolol for 6 weeks
Group F: banding and prazosin for 6 weeks

Table 5. Results of Left Ventricular Hypertrophy and Myocardial Norepinephrine, and Epinephrine Concentration in Different Rats after Abdominal Aortic Constriction and Release

	LVW	*BW*	*LVW/BW*	Left ventricular concentration		Total content × 10^3	
	mg	gm	mg/gm	*NE*	*EPI*	*NE*	*EPI*
				pg/mg	pg/mg	pg	pg
Group A: (n = 13)	879 ± 11	449 ± 9	1.96 ± 0.01	85.1 ± 5.8	5.6 ± 2.1	76.3 ± 6.7	5.0 ± 2.0
Group B: (n = 10)	999 ± 11	415 ± 9	2.41 ± 0.01	52.0 ± 5.4	1.0 ± 0.3	51.6 ± 5.9	1.0 ± 0.3
Group C: (n = 14)	995 ± 11	469 ± 9	2.12 ± 0.01	66.6 ± 3.1	0.5 ± 0.1	66.5 ± 3.9	0.5 ± 0.1
Statistical Significance (P ¡ 0.05)	A vs B, C	B vs C	A vs B, C B vs A, C C vs A, B	A vs B, C B vs A, V C vs A, B	A vs B, C	A vs B B vs A, C C vs B	A vs B, C

Note: Values are mean ± SD

Abbreviations: *LVW*: left ventricular weight
BW: body weight
NE: norepinephrine
EPI: epinephrine
Group A: control group
Group B: banding for 6 weeks
Group C: banding for 2 weeks and released for 4 weeks

and functional abnormalities in the cardiovascular system. Acute aortic constriction causes remarkable hemodynamic changes, including elevation of the pressure in the proximal portion, which has been attributed by a narrowing of the aortic lumen, a sudden increase in aortic impedance and a decrease in compliance (Symbas *et al.*, 1983; Salgado and Krieger, 1986; Salgado and Salgado, 1989). In this study, prolonged aortic constriction in Group B caused a significant increase in pulse pressure, and a decrease in heart rate and cardiac output. On the other hand, a long-term high afterload challenge, such as high pulse pressure, low *HR*, low *CO*, or high impedance, was noted in Group B to induce an increase in *Wo*, *Wo/Wt*, *Pb* and *Pf*. These changes could be minimized if constriction was relieved early on in Group C. It has been implicated that the normalization of aortic pressure and pulse pressure may occur, if aortic narrowing occurs early on. The increase in pulse pressure due to aortic constriction could also be prevented if vasodilators, such as propranolol, captopril and prazosin, were given when aortic constriction occurred. These findings were found in the rats in Groups D, E and F. The acute and subacute mechanical obstruction of the aorta is not the only possible reason for an elevation in pressure. Prolonged procedure and renal arterial ischemia which activates the renin-angio-

Table 6. Results of Left Ventricular Hypertrophy and Myocardial Norepinephrine, and Epinephrine Concentration in Different Rats with Vasodilator Effects

	LVW mg	*BW* gm	*LVW/BW* mg/gm	Left ventricular concentration *NE* pg/mg	*EPI* pg/mg	Total content × 10^3 *NE* pg	*EPI* pg
Group A: (n = 13)	879 ± 11	449 ± 9	1.96 ± 0.01	85.1 ± 5.8	5.6 ± 2.1	76.3 ± 6.7	5.0 ± 2.0
Group D: (n = 10)	939 ± 11	404 ± 6	2.32 ± 0.01	58.7 ± 3.6	5.4 ± 1.2	55.8 ± 4.3	5.1 ± 1.1
Group E: (n = 12)	851 ± 10	371 ± 5	2.29 ± 0.01	55.7 ± 4.7	5.8 ± 1.0	47.3 ± 4.5	4.8 ± 0.8
Group F: (n = 11)	962 ± 12	409 ± 8	2.35 ± 0.01	67.3 ± 6.3	2.3 ± 0.4	64.0 ± 4.0	2.2 ± 0.4
Statistical Significance (P ¡ 0.05)	D vs E E vs D, F	A vs D, E, F	A vs D, E, F	A vs D, E, F D vs A E vs A, F F vs A, E	A vs F D vs F E vs F	A vs D, E D vs A E vs A, F F vs E	

Note: Values are mean ± SD.

Abbreviations: *LVW*: left ventricular weight; *BW*: body weight; *NE*: norepinephrine; *EPI*: epinephrine

Group A: control group
Group D: banding and captopril for 6 weeks
Grpup E: banding and propranolol for 6 weeks
Group F: banding and prazosin for 6 weeks

tensin system and the secretion of renin may cause an elevation in blood pressure (Symbas *et al.*, 1983; Salgado and Krieger, 1986). A previous study demonstrated an effective vasopressor role of vasopressin in the genesis of acute and subacute hypertension (Haddad *et al.*, 1996). In a previous study on a rodent heart, the β-myosin heavy chain was expressed strongly related to the arterial pressure imposed on the left ventricle. These findings suggested that the renin-angiotensin system is not the only factor involved in cardiac hypertroply or β-myosin heavy chain expression in some models of hypertension (Haddad *et al.*, 1996). Although vasodilators were adminstered during aortic constriction, we observed an increase in aortic pressure in rats which received captopril or prazosin. The rats which received propranolol had normal aortic and pulse pressure but slow heart rates and lower cardiac output. This indicates that propranolol has a stronger effect on cardiac contraction and heart rate. Increased pressure or volume work load in the left ventricle may be associated with stretching of the ventricular wall and increased release of neurotransmitters that directly affect the growth of cardiac myocyte, subsequently leading to secondary cardiac hypertrophy. Based on a study on adult Sprague-Dawley rats, cardiac hypertrophy induced by abdominal constriction was proposed to be mediated by the angiotensin type I receptor resulting in upregulation of the cardiac angiotensin type I and transforming growth factor-B genes (Everett *et al.*, 1994).

With an increase in hemodynamic challenge and associated neurohumoral responsive reactions, the adaptive changes of myocardium from dysfunction during compensation to decompensation were noted (Meerson, 1969). Changes in cardiac size, composition and function in the myocardium and myocytes usually depend on the cardiac status of hyperfunction, compensation or decompensation. If hemodynamic challenge is the primary factor involved in the initiation and maintenance of cardiac hypertrophy (Cooper *et al.*, 1985), then a reduction of hemodynamic challenge may cause obvious but reversible alterations in cardiac hypertrophy, hyperfunction, and dysfunction (Cooper and Tomanek, 1982; Thompson *et al.*, 1984). This study demonstrated that relief of aortic constriction after a period of constriction actually reversed hemodynamic changes, including *HR*, *SV*, *CO*, *Rp*, aortic impedance, and compliance. However, some cardiac function including *fo*, *Wo*, *Wo/Wt*, *Pb* and *Pf*, were still abnormal even after constriction ended. A hypertrophied heart with depleted ventricular NE and EPI concentration still remained lower than normal even 4 weeks after aortic constriction in group C ended. The depletion of NE and EPI in the left ventricle was also noted in rats which received vasodilators during aortic constriction. Therefore, we suggest that a reduction in afterload due to either mechanical or pharmacologic action can keep a hypertrophied heart from deteriorating, but that already present compensatory changes in the myocardium are irreversible. The persistence of cardiac hypertrophy, combined with ventricular catecholamine depletion, implies the occurrence of cardiac decompensation and heart failure. Constriction of the aortic lumen above the renal arteries reduces the renal blood flow and elicits a prompt reaction in the renin-angiotensin system (Yagi *et al.*, 1968; Symbas *et al.*, 1983; Morgan and Baker, 1991; Kromer and Riegger,1985; Salgado and Salgado,1989; Baker *et al.*, 1990; Sadoshima and Izumo, 1993). Moreover, it also causes an increase in plasma catecholamines and the renin concentration in systemic circulation (Gelman *et al.*, 1990; Symbas *et al.*, 1983; Normann *et al.*, 1983). However, the complexity of neurohumoral response for vasopression and/or hypertrophic role on the myocardium still remains controversial (Morgan and Baker,1991; Salgado *et al.*, 1994; Sen *et al.*, 1974, 1977, 1981; Sen and Tarazi, 1983).

In this study, we clearly demonstrated that captopril, propranolol and prazosin improved aortic impedance (*Z1*, *Zc*), compliance, *fo* and cardiac performance (*Wo*, *Wo/Wt*, *Pb*, *Pf*, *Pb/Pf*) in rats after aortic constriction. These results suggest that increasing pulse pressure can be corrected by these medications; however, low cardiac output and high peripheral resistance can not be changed. The persistence of cardiac hypertrophy with depletion of ventricular catecholamines and low ventricular catecholamines was similar to that rats after aortic constriction without administration of captoten, propranolol or prazosin. The renin-angiotensin system and sympatho-adrenergic system ($\alpha 1$, β) may function as vasopressor and inotropic factor to myocardium in rats after aortic constriction. Regulation of the afterload on secondary cardiac hypertrophy is resulting form multiple factors involved. However, neither the renin-angiotensin system nortse sympatho-adrenergic system is the sole factor involved in the pathogenesis of myocardial hypertrophy.

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Changes in Rats after Aortic Constriction

老鼠的流體力學及神經活性在主動脈窄縮後的變化

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摘 要

心臟肥厚是長期增加心臟工作負荷的代償性作用。它包括血流動力的變化與神經荷爾蒙的反應，所相關的心臟功能亢進。問題是：何者扮演啟動的因素？何者維持整個心臟肥厚過程的進行？我們在SD老鼠，以腹主動脈窄縮來增加心臟的壓力負荷及活化神經荷爾蒙的作用，以造成續發性心臟肥厚。實驗共分七組，A組接受假手術當對照組，B組接受主動脈窄縮 6 週， C 組接受主動脈窄縮 2 週後再並解除窄縮 4 週， D, E及 F 組接受主動脈窄縮並分別以 captopril, propranolol 及 prazosin 治療 6 週。在靜態血流動力部份，主動脈窄縮能降低心臟輸出量及加寬脈博壓。此現象在窄縮解除後即可恢復，而captopril, propranolol及prazosin的治療，僅能恢復變寬的脈博壓。在動態血流動力部分，主動脈窄縮增加主動脈的阻抗(impedance)，心臟性能負荷及減少主動脈的可容性(compliance)。解除窄縮使主動脈的阻抗及可容性回復正常，而對心臟性能的負荷僅僅只有改善的程度。但在藥物治療組，若與僅接受主動脈窄縮六週組比稱，則主動脈的阻抗可容性及心臟性能負荷都已達有統計意義改善。在所有的實驗鼠組，肥厚的心臟及心室心肌中catecholamine的持續流失，仍然不見改善。從以上實驗數據闡明：主動脈窄縮所誘發的續發性心臟肥厚是多重因素參與的。然而，既不是renin-angiotensin 系統也不是 sympatho-adrenergic 系統所能單獨調控的，雖然它們都俱有促成心肌肥厚的效能。