ASSESSMENT OF RELATIONSHIP BETWEEN THE PATTERN OF HYPERTROPHY AND THE FUNCTION OF LEFT VENTRICLE IN PATIENTS WITH CHRONIC AORTIC REGURGITATION

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Pre- and postoperative echocardiograms of 64 patients with chronic aortic regurgitation who had undergone isolated aortic valvular replacement (AVR) were studied. These patients were divided into 3 groups as follows: (1) Group A patients who had preoperative end-diastolic radius to wall thickness ratio (R/Thd) ≤ 3 . (2) Group B1 patients who had preoperative $R/Thd > 3$ and end-systolic radius to wall thickness ratio (R/Ths) < 2 . (3) Group B2 patients who had preoperative $R/Thd > 3$ and $R/Ths \geq 2$. Using this classification we assessed the relation between the pattern of hypertrophy and left ventricular (LV) function and the reversibility of LV dysfunction following AVR. Preoperatively, ejection fraction (EF) during handgrip exercise was unchanged in Group A ($\% \Delta EF: -2.8 \pm 7.1\%$) and significantly decreased in Groups B1 ($-17.0 \pm 5.8\%$) and B2 ($-20.2 \pm 4.6\%$). In the late postoperative period, however, it was, $-1.2 \pm 3.3\%$, $-2.0 \pm 4.6\%$, and $-17.7 \pm 8.6\%$ in Groups A, B1, B2, respectively. Preoperatively the slope of end-systolic wall stress/volume (ESWS-ESV relation was 1.96 ± 0.43 in Group A ($p < 0.01$ vs Group B2, NS vs Group B1), 1.54 ± 0.38 in Group B1 (NS vs Group B2) and 1.17 ± 0.47 in Group B2. It was stressed that a good relationship existed between the pattern of hypertrophy and function as well as the reversibility of LV dysfunction following AVR.

PATIENTS with chronic aortic regurgitation (AR) may remain asymptomatic for many years even in the presence of significant impairment of myocardial contractility. This has led to much discussion concerning the appropriate timing of aortic valve replacement (AVR).¹⁻⁶

Echocardiographic indexes would be useful predictors for the postoperative normalization of the dimension and the function of left ventricle, as they involve noninvasive procedures and allow the possibility of serial measurement.

Key words:

ESWS-ESV relation
Handgrip exercise test
Chronic AR

Several echocardiographic indexes have been proposed but they remain controversial.^{3,5-7} It would also be useful to be able to assess the dimension and function of the left ventricle (LV) following surgery from preoperative pattern of hypertrophy. The pattern of hypertrophy of LV in AR, one of the LV volume overload diseases, is known as eccentric hypertrophy.⁸ The echocardiographic findings of the left ventricle of this disease, however, are not consistent but exhibit a variety of patterns.

The present study was undertaken to classify the patterns of hypertrophy of LV in patients with AR by mean of M-mode echocardiography and to try to assess the relationship between the

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pattern of hypertrophy and the function of LV. We also examined the relation between the pre-operative pattern of hypertrophy of LV in AR and the LV size, mass and function after AVR.

METHODS

Patients: The study group consisted of 64 of 178 patients with chronic aortic regurgitation who underwent isolated AVR at our institute from March 1979 to February 1987. Only patients with high-quality pre- and postoperative M-mode echograms were included. Those patients with obstructive coronary disease, aortic valvular stenosis (as judged by operative findings or a peak transvalvular gradient exceeding 20 mmHg) and mitral stenosis were excluded. Only 8 cases with moderate mitral regurgitation secondary to annular dilatation that were not severe enough to require valve replacement were included. None of the patients had electrocardiographic or historical evidence for perioperative infarctions. Those patients who did not reveal chamber dilatation ($LVDd < 55$ mm) were excluded.

Patients' ages ranged from 13 to 71 years (mean 44 ± 11 (SD) years). Forty-nine of 64 patients were male. By New York Heart Association (NYHA) classification, 47 (73.4%) and 17 (26.6%) patients were class 1-2 and 3-4, respectively. Fifty-two patients (81.3%) received preoperative cardiac catheterization and angiogram. The degree of aortic regurgitation was assessed from supra-valvular aortogram by the classification of Hunt⁹ and it was graded as 3 in 14 (26.9%) and 4 in 38 (73.1%) patients.

The remaining 12 patients (18.6%) had clinical signs of isolated moderately severe aortic regurgitation which was diagnosed only by echocardiography and/or Doppler echocardiography.

The prosthetic valves implanted were Ionescu-Shiley (37.5%), St. Jude Medical (18.7%), Bjork-Shiley (15.6%), Carpentier Edwards Pericardial Xenograft (12.5%), and others (15.7%). Annuloplasties were performed in 8 patients with moderate mitral regurgitation simultaneously with AVR.

Echocardiography: Echocardiograms were obtained with a Toshiba SSH 60A ultrasonograph and a 3.75 MHz transducer. Serial M-mode echocardiograms were recorded in slight left lateral decubitus position. LV echograms were recorded at the level of the chorda of the mitral valve with two dimensional echo guidance. Both long axis

and transverse scans were performed to ensure the demonstration of the greatest LV internal dimension. LV dimension at end-diastole (LVDd) was measured at the R wave of the echocardiogram, and the dimension at end-systole (LVDs) was measured at the time of the first high-frequency component of the second heart sound. Posterior wall thickness (Thd and Ths) was measured at end-diastole and end-systole from the leading edge of the epicardial echo. Echocardiograms with markedly paradoxical septal motion were excluded from the postoperative analysis.

Echocardiographic indexes were calculated from the preceding measurement by the following formulae:

FS (fractional shortening)

$$= [(LVDd - LVDs) / LVDd] \times 100$$

CSA (cross sectional area)

$$= \pi [(LVDd/2) + PWThd]^2 - \pi (LVDd/2)^2$$

R/Thd (end-diastolic radius to wall thickness ratio) = $LVDd / (2 \times Thd)$

R/Ths (end-systolic radius to wall thickness ratio) = $LVDs / (2 \times Ths)$

Handgrip exercise: Eighteen of 64 patients who underwent AVR from September 1985 to 1987 entered this prospective study. Four of 18 patients could not receive early (about 1 month) postoperative exercise test because of markedly paradoxical septal motion. Twenty-three patients who underwent AVR from May 1979 to February 1986 received late (mean 3.1 years in the follow up) postoperative exercise study. Normal healthy subjects (mean age of 41 years old) served as a control group.

Each patient was asked to sustain 33% of maximum voluntary compressive force, as previously determined on a hand dynamometer (SMEDLEYS DYNAMO METER), for 3 min. Patients were instructed to breath normally throughout the test period. Electrocardiograms, cuff blood pressure, serial carotid pulse, phonocardiograms and M and B mode echocardiograms were obtained before the test and during the 3 min of the handgrip exercise. Ejection fraction during exercise and at rest were obtained from the following:

EF (ejection fraction)

$$= [(EDV - ESV) / EDV] \times 100$$

EDV (end-diastolic volume)

$$= (\pi/6) \times (5.90 + 0.98 LVDd) \times (LVDd)^2$$

Fig.1. An example of end-systolic wall stress/volume relationship in a patient with aortic regurgitation.

$$\text{ESV (end-systolic volume)} = (\pi/6) \times (4.18 + 1.14 \text{ LVDs}) \times (\text{LVDs})^2 \cdot 10$$

Percent change of ejection fraction was determined as follows:

$$\% \Delta \text{EF} = [(\text{EF}_{\text{ex}} - \text{EF}_{\text{rest}}) / \text{EF}_{\text{rest}}] \times 100$$

Pressure Volume and Stress Volume Relationship: After completion of the handgrip exercise test and return of heart rate, blood pressure, and echocardiographic findings to control values, the afterload was reduced with sodium nitroprusside. Four patients excluded from the postoperative exercise study and 1 patient with low systolic blood pressure could not receive postoperative nitroprusside study. Echocardiograms were recorded before, as control, and every 5 min after the initiation of an intravenous infusion of the drug in 13 subjects. It was started at a rate of $0.4 \mu\text{g/kg/min}$ and increased every 10 min to a dosage sufficient to lower the peak systolic pressure (Pps) about 15–30 mmHg. A Dinamap Vital Signs Monitor (Nihon Kohden Inc.) was used to measure peak systolic pressure. The peak systolic pressure/end-systolic volume (ESV) relationship was obtained from cuff blood pressure and echocardiographic monitoring. The end-systolic wall stress (ESWS) and volume (ESV) relationship was obtained at the same time. The end-systolic meridional wall stress was calculated according to the method of Grossman¹¹

Fig.2. Three types of left ventricular shape in chronic aortic regurgitation. R/Thd = end-diastolic radius to wall thickness ratio; R/Ths = end-systolic radius to wall thickness ratio.

and Reichek¹² by the following equation:

$$\begin{aligned} \text{ESWS (dyn/m}^2\text{)} &= 1.33 \times 10^3 \times \text{Pps} \times \text{LVDd} / 4\text{Ths} \\ &\times (1 + \text{Ths} / \text{LVDs}) \end{aligned}$$

where Pps = systolic blood pressure by cuff measurement. A linear regression line was constructed by plotting the relative end-systolic volume against the corresponding end-systolic wall stress by regression analysis (Fig. 1). The slope of the ESWS-ESV relation was used to assess myocardial contractility.

At the same time peak systolic wall stress (PSWS) was calculated as follows^{13,14}:

$$\begin{aligned} \text{PSWS (dyn/cm}^2\text{)} &= [[(0.334 \times \text{Pps} \times \text{LVDd}) / \text{Thd} \times (1 + \text{Thd} / \text{LVDd})] \times 0.86 - 27] \times 10^3 \end{aligned}$$

Statistical Analysis: All values were expressed as mean $\pm$ SD. Changes from rest to exercise or pre- to postoperative condition was tested by Student's paired t test. For comparison of measurements of each group and control group, an unpaired t test was used. Where more than 2 groups were compared, analyses of variance were performed and if analysis suggested that the groups differed significantly from one another ($p < 0.05$), multiple range testing comparing individual groups to one another was performed. A p-value less than 0.05 was considered significant.

RESULTS

Classification of the pattern of hypertrophy: There was a variety of size and wall thicknesses

TABLE I PREOPERATIVE ECHOCARDIOGRAPHIC DATA IN THE THREE GROUPS OF PATIENTS WITH AORTIC REGURGITATION AND NORMAL SUBJECTS

	Group A	Group B ₁	Group B ₂	Control subjects
No.	26	29	9	12
Age (yr)	44 ± 12	43 ± 12	46 ± 7	41 ± 11
BSA (m ²)	1.60 ± 0.14	1.59 ± 0.17	1.50 ± 0.25	1.69 ± 0.23
LVDd (cm)	7.0 ± 0.6**	7.1 ± 0.7**	8.9 ± 1.2**	4.8 ± 0.3
LVDs (cm)	5.0 ± 0.6**	5.3 ± 0.8**	7.6 ± 1.3**	3.2 ± 0.3
CSA (cm ²)	34.3 ± 6.7**	27.3 ± 5.5**	36.3 ± 6.5**	14.1 ± 1.6
FS (%)	28.1 ± 5.9**	26.1 ± 5.9**	14.5 ± 4.4**	33.9 ± 4.5
R/Thd	2.65 ± 0.33**	3.41 ± 0.33**	3.90 ± 0.47**	3.03 ± 0.36
R/Ths	1.31 ± 0.23*	1.58 ± 0.23**	2.56 ± 0.36**	1.13 ± 0.22

Values represent group means ± 1 S.D.

BSA = body surface area; LVDd = left ventricular end-diastolic dimension; LVDs = left ventricular end-systolic dimension; CSA = cross sectional area; FS = fractional shortening; R/Thd = end-diastolic radius to wall thickness ratio; R/Ths = end-systolic radius to wall thickness ratio.

*p < 0.05, **p < 0.01 vs corresponding control values.

Fig.3. Preoperative (clear bars), early postoperative (hatched bars), and late postoperative (black bars) values in LVDd, CSA and FS for subjects of groups A, B1 and B2. Brackets indicate standard deviation. The dashed line indicates the mean value of normal subjects.

*p < 0.05, **p < 0.01; compared to the preoperative values.

†p < 0.05, ††p < 0.01; compared to the normal values.

in patients with AR. These were summarized and classified into 3 groups (A, B1, B2), according to the radius to wall thickness ratio (Fig. 2). Left ventricles in the patients in group A revealed a compensated type of hypertrophy (R/Thd ≤ 3). Thickening of the posterior wall as well as the chamber dilatation of LV was detected in this group. Left ventricles in the patients in group B exhibited an eccentric type of hypertrophy (R/Thd > 3). This group was further divided into two subgroups (B1, B2) according to R/Ths.

Table I lists the mean ± standard deviation of each preoperative variable in the 3 groups of 64 patients with AR, and 12 normal subjects. Preoperative LV end-diastolic dimensions (LVDd) were higher than normal control values in groups A (7.0 ± 0.6 cm), B1 (7.1 ± 0.7 cm), and B2 (8.9 ± 1.2 cm) (p < 0.01). The mean values of cross sectional area (CSA), used as an index of LV mass, were also higher than normal in the 3 groups (34.3 cm², 27.3 cm², 36.3 cm², respectively). The preoperative fractional shorten-

Fig. 4. End-systolic and peak-systolic stress in group A, B1, B2 and normal control group.

ing (FS) was lower than normal in groups A ($28.1 \pm 5.9\%$), B1 ($26.1 \pm 5.9\%$) ($p < 0.05$) and B2 ($14.5 \pm 4.4\%$) ($p < 0.01$). The patients in these 3 groups exhibited LV dilatation and hypertrophy, but marked reduction in pump function was noted only in group B2. Fig. 3 demonstrates the changes in LVDd, CSA and FS in 44 patients with complete preoperative, early and late postoperative data in the 3 groups. It was noted that the dilatation of LV was manifested in group B2 and the FS in all 3 groups was low in the early postoperative period (about 1 month). In the late follow up a mean of 2.7 years after valve replacement, groups A, B1, and B2 showed a significant decrease in LVDd and CSA, but the values still remained markedly higher than normal in group B2. The FS in group B2 did not exhibit significant increase in late follow up and also remained lower than normal. Although the regression of LV hypertrophy was incomplete in both group A and group B1, LV chamber size and pump function were completely normal in the late postoperative period in these groups (Fig. 3).

Preoperative end-systolic and peak-systolic wall stress were calculated in 12 normal subjects and 20 patients belonging to groups A, B1 and B2 (Fig. 4). The end-systolic stresses in groups A, B1, and B2 were 80.7 ± 19.9 , 115.1 ± 18.7 , 206.8 ± 41.7 , $\times 10^3 \text{ dyn/cm}^2$, respectively, and

significantly higher than that of normal control ($56.6 \pm 9.0 \times 10^3 \text{ dyn/m}^2$). It was noted that the value in group B1 remained relatively low though it was significantly higher than that in group A ($p < 0.01$). In contrast, patients in groups B1 and B2 had markedly high peak-systolic wall stresses (198.8 ± 24.7 , 248.4 ± 54.8 , $\times 10^3 \text{ dyn/m}^2$, respectively) and there were no significant differences between them. There were also no significant differences observed between peak-systolic stresses in group A and the normal control group.

Handgrip exercise testing: The individual results and the mean value of heart rate, systolic blood pressure, ejection fraction at rest and during maximal exercise in the patients in groups A, B1 and B2 are shown in Tables II (preoperative data) and 3 (postoperative data). Heart rate and systolic blood pressure were significantly increased in all groups except group B2 during exercise. In control subjects, ejection fraction increased significantly during handgrip exercise ($67.3 \pm 5.5\%$ at rest to $68.4 \pm 5.5\%$ with exercise) ($p < 0.05$). In contrast, ejection fraction was unchanged during exercise in group A ($60.5 \pm 8.1\%$ to $58.5 \pm 6.4\%$) and significantly decreased in groups B1 ($46.0 \pm 14.6\%$ to $38.1 \pm 12.0\%$; $p < 0.01$) and B2 ($39.2 \pm 9.7\%$ to $31.1 \pm 7.7\%$; $p < 0.01$) in the preoperative study (Table II). The same findings were observed in

TABLE II PREOPERATIVE DATA OF STRESS-VOLUME RELATION AND HANDGRIP EXERCISE IN 18 PATIENTS AND 12 NORMAL SUBJECTS

Case	Age (yr)	BSA (m ²)	End-Systolic Wall stress-Volume relation			Handgrip exercise data					
			Slope (m)	Intercept (Vo)	HR rest (beat/min)	HR ex (beat/min)	Ps rest (mmHg)	Ps ex (mmHg)	EF rest (%)	EF ex (%)	% ΔEF (%)
Group A											
1.	54	1.73	2.44	16.2	45	55	123	168	74.4	69.5	-6.6
2.	41	1.50	1.69	18.4	66	68	152	163	68.2	63.5	-6.7
3.	39	1.77	2.66	30.2	75	87	117	145	58.1	55.3	-4.8
4.	39	1.73	1.49	29.5	68	75	138	158	56.3	52.4	-6.9
5.	35	1.48	2.02	38.4	88	95	110	130	59.3	60.3	1.7
6.	24	1.80	2.08	16.6	55	73	130	167	63.0	61.7	-2.1
7.	45	1.76	1.78	62.3	67	83	144	184	56.8	51.4	-9.5
8.	64	1.60	1.50	21.8	77	78	175	185	47.6	53.5	12.4
Mean	43	1.67	1.96	29.2	68	77**	134	164**	60.5	58.5	-2.8
S.D.	12	0.13	0.43	15.5	12	12	10	14	8.1	6.4	7.1
Group B ₁											
1.	53	1.74	1.32	34.7	65	96	145	184	50.8	42.5	-16.3
2.	35	1.70	1.27	46.8	58	76	139	160	51.9	38.5	-26.0
3.	32	1.67	1.43	72.6	83	125	135	166	32.2	29.3	-9.0
4.	53	1.49	1.72	36.3	68	76	141	166	58.7	48.3	-17.7
5.	41	1.70	1.24	26.5	78	91	117	140	23.8	19.1	-19.7
6.	40	1.34	2.23	27.3	81	88	127	166	58.7	50.9	-13.3
Mean	42	1.61	1.54	40.7	72	90**	134	164**	46.0	38.1**	-17.0
S.D.	9	0.16	0.38	17.3	10	18	10	14	14.6	12.0	5.8
Group B ₂											
1.	39	2.04	1.29	122.8	115	125	152	170	51.9	40.6	-21.8
2.	40	1.56	1.03	129.2	63	107	133	150	31.7	23.5	-25.9
3.	58	1.44	1.50	63.8	58	72	156	178	41.6	34.4	-17.3
4.	44	1.37	0.83	77.1	82	121	130	136	31.5	26.6	-15.6
Mean	45	1.60	1.16	98.2	80	106	143	159*	39.2	31.3**	-20.2
S.D.	9	0.30	0.29	32.6	26	24	13	19	9.7	7.7	4.6
Normal Control Group											
1.	38	1.73	—	—	65	80	103	137	56.1	56.6	0.9
2.	63	1.51	—	—	64	79	92	188	69.2	69.9	1.0
3.	33	1.81	—	—	50	60	109	118	58.7	59.8	1.9
4.	34	1.79	—	—	64	67	105	134	67.2	68.1	1.3
5.	52	1.47	—	—	71	88	128	195	70.5	68.6	-2.7
6.	32	1.85	—	—	72	72	137	153	64.6	67.2	4.0
7.	30	1.87	—	—	65	87	113	133	66.1	67.9	2.7
8.	30	1.80	—	—	58	69	106	130	68.7	72.2	5.1
9.	41	1.40	—	—	73	83	111	115	69.0	70.5	2.2
10.	41	1.51	—	—	75	91	113	149	76.0	76.9	1.2
11.	58	1.39	—	—	68	68	97	117	69.9	72.9	4.3
12.	39	2.11	—	—	75	83	120	171	71.5	69.7	-2.5
Mean	41	1.69	—	—	68	111**	111	145**	67.3	68.4*	1.6
S.D.	11	0.23	—	—	6	13	13	27	5.5	5.5	2.4

EF = ejection fraction; ex = exercise; HR = heart rate; Ps = systolic pressure; % ΔEF = percent change of ejection fraction from rest to exercise.

*p < 0.05; **p < 0.01 vs corresponding resting values.

the early postoperative data (Table III). Tables II and III also show the average percent changes in ejection fraction (%ΔEF) in each group. Pre- and early postoperative %ΔEF in the 3 groups are shown in Fig. 5. All 3 groups indicated negative

values with the smallest change in group A. The control groups showed a positive but small value ($1.6 \pm 2.4\%$). Significant differences ($p < 0.01$) for the analysis of variance in the 3 groups were present both in pre- and early postoperative data,

TABLE III EARLY POSTOPERATIVE DATA OF STRESS-VOLUME AND HANDGRIP EXERCISE IN 14 PATIENTS

	Group A	Group B ₁	Group B ₂
No.	6	4	4
Slope-m	2.51 ± 1.00	1.26 ± 0.32	1.17 ± 0.47
Intercept-Vo	18.9 ± 12.0	28.9 ± 25.3	49.4 ± 48.8
HR rest (beat/min)	84 ± 10	87 ± 13	85 ± 12
HR ex (beat/min)	88 ± 11	94 ± 11	93 ± 10
Ps rest (mmHg)	119 ± 11	113 ± 4	124 ± 13
Ps ex (mmHg)	139 ± 15*	138 ± 13*	153 ± 12
EF rest (%)	52.8 ± 14.4	39.1 ± 10.0	30.4 ± 13.2
EF ex (%)	52.1 ± 14.5	33.1 ± 10.5**	19.8 ± 11.8*
%EF (%)	-1.6 ± 4.5	-16.9 ± 8.9	-37.8 ± 13.9

Abbreviations as in Table 1 and 2.

p* < 0.05; *p* < 0.01 vs corresponding resting values.

Fig. 5. Preoperative (clear bars) and early postoperative (hatched bars) values in %ΔEF in the three groups and normal control value.

and the significance of intergroup differences are shown in Fig. 5. Although groups B1 and B2 exhibited a significantly greater change than group A (*p* < 0.01), there was no significant difference between groups B1 and B2 preoperatively. However, group B2 showed a significantly

greater change than group B1 postoperatively (*p* < 0.05) which showed mean percent change of -37.8%. There were no significant differences between pre- and early postoperative data in all 3 groups.

%ΔEF during handgrip exercise in the late

Fig.6. % Δ EF in the three groups in the late postoperative period and normal control value.

Fig.7. Slope of end-systolic wall stress/volume relation in patients in group A, B₁ and B₂. Left: preoperative data; right: early postoperative data are shown.

postoperative period in 19 patients belonging to the 3 groups are shown in Fig. 6. It was noted that group B₁ revealed smaller change ($-2.0 \pm 4.6\%$) in comparison to larger change in early

postoperative period, group B₂ showed greater change at the same time with mean % Δ EF of -17.7% .

Stress Volume relationship: As shown in

TABLE IV LV DIMENSION, MASS AND PUMP FUNCTION BEFORE AND AFTER AVR IN THE THREE GROUPS

	Group A	Group B ₁	Group B ₂
<i>LV dimension</i>			
pre op.	increased	increased	markedly increased
early post op.	normal	increased	increased
late post op.	normal	normal	increased
<i>LV mass</i>			
pre op.	markedly increased	increased	markedly increased
early post op.	increased	increased	markedly increased
late post op.	increased	increased	markedly increased
<i>Pump function</i>			
pre op.	depressed	depressed	markedly depressed
early post op.	depressed	markedly depressed	markedly depressed
late post op.	normal	normal	markedly depressed

TABLE V SYSTOLIC FUNCTIONAL RESERVE AND MYOCARDIAL CONTRACTILITY BEFORE AND AFTER AVR IN THE THREE GROUPS

	Group A	Group B ₁	Group B ₂
<i>Systolic functional reserve</i>			
pre op.	depressed	markedly depressed	markedly depressed
early post op.	normal	markedly depressed	markedly depressed
late post op.	normal	depressed	markedly depressed
<i>Myocardial contractility</i>			
pre op.	fair	poor	very poor
early post op.	good	poor	very poor

Fig. 1, end-systolic wall stress correlated well with end-systolic volume. Preoperatively, the slope of the ESWS-ESV relationship was steeper in group A (1.96 ± 0.43) than in group B2 (1.16 ± 0.29) ($p < 0.01$) (Table II, Fig. 7), although there were no significant differences between groups A and B1 (1.54 ± 0.38) and between groups B1 and B2. However in the post-operative period, the slope of this relationship in group A (2.51 ± 1.00) was steeper than for groups B1 (1.26 ± 0.32) and B2 (1.17 ± 0.47) and there was no significant difference between the value in groups B1 and B2 (Fig. 7).

DISCUSSION

In this study, we have classified the pattern of hypertrophy of LV in patients with chronic aortic regurgitation in to 3 groups (A, B1, B2) according to the radius to wall thickness ratio (R/Thd and R/Ths) and assessed the relation between the pattern of hypertrophy and LV

function as well as the reversibility of LV dysfunction and hypertrophy after valve replacement. The results suggested that such classification was useful in assessing the LV function and at the same time predicting the reversibility of LV dysfunction and hypertrophy after AVR.

Three types of the pattern of hypertrophy of LV in patients with chronic aortic regurgitation: Although there are various studies¹⁵⁻¹⁸ about the factors influencing the pattern of hypertrophy, little is known about these factors. Grossman¹⁵ et al speculated from their clinical data that hypertrophy developed to normalize systolic but not diastolic wall stress. To account for the different patterns of hypertrophy, they also proposed the hypothesis, that LV pressure overload as the primary stimulus led to the parallel replication of sarcomeres and concentric hypertrophy. On the other hand, LV volume overload and increased end-diastolic wall stress as the primary stimulus led to serial replication of sarcomeres and eccentric hypertrophy which

would be followed by increased peak systolic wall stress and wall thickening. We have classified the dilated left ventricles in AR into 3 groups according to the R/Th. The R/Th, an index of the LV volume/mass ratio, reflects the degree to which the LV muscle mass is appropriate for a given chamber volume.² Grant⁸ considered that a ventricle with eccentric hypertrophy was a magnified normal ventricle, and thus, the R/Th was normal.

It means that the deviation from the normal R/Th reflects a failure of hypertrophy to match the volume load imposed on the left ventricle.

The volume/mass ratio in group A, defined as the $R/Thd \leq 3.0$, is lower than normal. As shown in Fig. 6, calculated peak systolic wall stress in this group stayed in the normal range with the aid of compensated hypertrophy. In contrast, in group B, $R/Thd > 3.0$, and thus the volume mass ratio is normal or more than normal. In this group compensated hypertrophy was thought to be insufficient and the value of peak systolic wall stress was significantly high compared with group A ($p < 0.01$). Although there was no difference in peak-systolic wall stress between groups B1 and B2, the value of end-systolic wall stress in group B1 remained lower ($p < 0.01$) and its wall motion appeared relatively hyperkinetic in contrast to hypokinetic wall motion in group B2. These data confirm that end-systolic stress is literally the afterload that limits ejection.¹² Remembering peak-systolic stress normally occurs at a R/Th quite comparable to $R/Thd^{8,13}$ we can easily understand our actual stress data.

The decrease in the preoperative FS in group B2 (Fig. 4) was associated with a large increase in end-systolic wall stress (Fig. 6), that is consisted with the idea of force-velocity-shortening relationships.¹⁹ Early postoperatively, no improvement in FS was detected in any of the 3 groups (Fig. 4). Boucher²⁰ et al also reported that EF decreased early after the correction of AR and that late postoperatively it returned toward preoperative values. The LVDd significantly decreased early after AVR in all 3 groups (Fig. 4). As Boucher et al noted, the early postoperative reduction in FS or EF might be due to the effect of dominant preload change at this time.²⁰ The improvement of FS or EF late after AVR, may be a result of the reduced afterload with gradual improvement in contractile function, possibly related to the regression of left ventricular hypertrophy.

Pattern of hypertrophy of LV and EF response to exercise: In patients with AR, the resting measurements of LV function may remain normal, despite development of LV dysfunction during stress interventions.^{1,21-23} Recently, many investigators have reported abnormal EF response to exercise in patients with AR, and stressed the usefulness of the exercise EF response in early detection of LV dysfunction.^{1,22,24,25} Although the association between the change in exercise EF and the non-invasive predictors have been reported,^{26,27} our study is unique in its assessment of the relation between the pattern of hypertrophy of LV and EF response to exercise.

The results of the present study indicated that there existed a good correlation between the pattern of hypertrophy of LV and exercise EF response. Our data are consistent with those of Goldman et al²⁷ and Lewis et al²⁸. In their study, patients who showed a decrease in EF during exercise had a greater R/Th. Goldman et al²⁷ and Greenberg et al²⁵ who estimated systolic wall stress by M-mode echocardiography, suggested that exercise-induced LV dysfunction in patients with AR was the result of elevated LV systolic wall stress.

Previous reports have simply indicated that those patients whose ejection fraction decreased during exercise had significantly high systolic wall stress at rest.^{25,27,28} Our data from the categorization of the pattern of hypertrophy have given more information as to the relation between the exercise EF response and the systolic wall stress. Although changes in EF ($\% \Delta EF$) in the control group were significantly greater than in group A preoperatively, there was no significant difference in peak-systolic wall stress between them. Furthermore, though end-systolic wall stress in group B2 was significantly higher than in group B1, no significant change in EF was detected between the 2 groups preoperatively.

Greenberg et al²⁵ reported that the patients with AR whose EF fell during exercise had elevated resting end-systolic wall stress. On the other hand, Lewis²⁸, Iskandrian²⁹ and Goldman et al²⁷ observed that peak-systolic wall stress at rest was higher in patients with AR who had an abnormal exercise EF response. Although we cannot explain the exact mechanism, our data suggest that both end-systolic and peak-systolic wall stress may be important factors in determining the exercise response.

In the group of patients with greatly elevated

systolic wall stress or inadequate compensatory hypertrophy, the ventricle may be considered to reach easily the afterload mismatch and limitation of its preload reserve (deterioration of Frank-Starling mechanism).

Reversibility of LV dysfunction during exercise: Although many investigators have reported abnormal EF response to exercise in patients with AR and its usefulness in detecting LV dysfunction or identifying high risk group after AVR,^{1,20,22} only a few of them have studied the reversibility of exercise-induced LV dysfunction after surgery.^{1,19} Huikuri et al²¹ performed handgrip exercise test during catheterization on 17 patients with AR both preoperatively and one year after successful AVR. They observed a positive correlation ($r = 0.85$, $p < 0.001$) between the changes in the EF during pre- and postoperative exercise test and concluded that in patients with severely depressed EF during the preoperative exercise test, the ventricular response to exercise was not totally corrected after surgery. Our results are consistent with those of Huikuri. In the late postoperative period (average 2.7 years after AVR), the patients in group B1 with greatly depressed EF during pre- and early postoperative exercise test showed an improvement in response to exercise, but it was incomplete. Our results indicate that the reserve of systolic function of LV has been depressed preoperatively in the group of patients who had elevated systolic wall stress (group B1, B2), and the improvement does not completely occur even in the long follow up after surgery. Particularly in the group of patients with greatly elevated end-systolic wall stress (group B2), EF response to exercise was markedly depressed in the late postoperative period. Irreversible myocardial dysfunction was considered to have occurred in the patients of this group.

Goldman et al²⁷ and other investigators^{19,30} demonstrated that patients with AR who showed evidence of abnormal exercise EF response or elevated systolic wall stress preoperatively had a higher incidence of persistent LV dilatation and dysfunction after AVR. Our results indicate, however, that among many patients with abnormal exercise EF response preoperatively, only a small group with greatly elevated end-systolic wall stress (group B2) have persistent LV dysfunction in the late postoperative period.

Relationship between the pattern of hypertrophy and myocardial contractility: The LV end-systolic pressure/volume relationship (ESPVR)

has been proposed as a reliable index of myocardial contractility that is independent of preload and afterload.^{31,32} Since Grossman¹⁰ applied the LV end-systolic pressure/volume relationship to man for the assessment of myocardial contractility, several clinical studies on this subject have been performed. All of these parameters such as the end-systolic pressure/volume, length/tension, and stress/strain relations have been demonstrated to be linear in man³³⁻³⁵ as well as in experimental dogs.^{36,37} The slope of ESPVR is independent of preload, and mode of contraction. It incorporates afterload and may accurately reflect the inotropic state of the left ventricle.^{10,38,39}

We substituted peak systolic pressure (Pps) for end-systolic pressure (Pes), as was attempted by several investigators.^{40,41} Borow³³ has demonstrated an excellent correlation ($r = 0.984$) between the central aortic pressure and Dinamap measurement for peak systolic pressure.

Although ESPVR was linear for each subject in our study, we thought it reasonable to use the stress/volume relationship to compare and evaluate the myocardial contractility of hearts of different size and muscle mass, as suggested by Takahashi and Sasayama.^{40,42}

Borow and coworkers³⁹ demonstrated the linearity of the end-systolic wall stress/dimension relation and showed that an increase of ventricular inotropic state made the slope of the line steeper and produced a leftward displacement. However, there is a problem with end-systolic wall stress/volume (dimension) relation in that normalization of the volume (dimension) has not been accomplished. This is also true for ESPVR and future study on the matter is expected. The meaning of intercept (end-systolic volume at zero end-systolic wall stress) of the end-systolic wall stress/volume relation has not yet been determined, therefore we have analyzed only the slope of line of end-systolic wall stress/volume relation in the present study.

When altering systolic load using an agent, there is great concern contractility will be affected. Although the agent we used is thought to have little direct effect on myocardial contractility,⁴³ reflex may alter the contractility. Therefore, we took great care in the infusion of nitroprusside to avoid a rapid change in heart rate or systolic pressure. As a result, heart rate remained relatively constant and reflex might have at most a small effect contractility during nitroprusside infusion.

Another limitation on the assessment of myocardial contractile state by end-systolic stress/volume relation in this study is the difficulty in accurately measuring end-systolic volume and end-systolic stress. We used the first high frequency component of second heart sound to identify the end-systolic point. Although, as has been pointed out, the accuracy of echocardiographic measurement of left ventricular volume is inferior to angiographic measurement,⁴⁴ serial study to obtain pressure and volume data by this invasive procedure was impractical. Echocardiography not only is superior to angiography in this point but also provides accurate information about posterior wall thickness.

Abnormal septal motion occurs commonly after AVR and may invalidate some of the postoperative measurements. In this study, the echocardiograms that exhibited markedly paradoxical septal motion were eliminated from the analysis. Another factor that might induce an error in measurement of chamber volume using M-mode echocardiography is the changes in LV geometry in AR. However, Schuler et al⁴⁵ demonstrated a high correlation ($r = 0.92$) between postoperative echocardiographic and radionuclide estimates of ejection fraction in patients with AR who did not show paradoxical septal motion. There were no subjects with marked LV asynergy in our study and we used the formula of Gibson in calculating LV volume, so we believe that the geometrical factor was a minor one and it did not invalidate the assessment using M-mode echocardiography.

The fidelity of noninvasive measurement of end-systolic meridional wall stress is another difficulty. We used cuff systolic pressure to approximate true LV end-systolic pressure as has been reported elsewhere,^{11,35,42} and calculated end-systolic stress according to the method of Grossman¹¹ and Reichek¹² et al. Reichek demonstrated extremely good correlation between noninvasive and invasive measurement of end-systolic stress ($r = 0.97$) and cuff systolic pressure and end-systolic LV micromanometer pressure ($r = 0.89$). Our result for noninvasive end-systolic stress data in normal control group ($63.5 \pm 13.8 \times 10^3$ dyn/cm²; $n = 10$) was similar to the normal control data of Reichek et al ($64.8 \pm 19.5 \times 10^3$ dyn/m²; $n = 22$).

Our data clearly indicated that myocardial contractile state in group B2 was severely depressed preoperatively and the improvement of contractility in the early postoperative period

was recognized only in those patients with small wall stress associated with sufficiently compensated hypertrophy.

Table IV and V show the summary of the relation between the pattern of hypertrophy of LV in AR and function before and after surgery. Since we did not study the ESPVR in the late follow up, we could not know whether the early postoperative depression in myocardial contractility in group B1 would improve or not afterward. However, the dimension, mass, pump function and systolic functional reserve returned to nearly normal values in both group A and group B1 in the late follow up period. In contrast, there was no improvement in group B2 even late after AVR, so the preoperative myocardial change in this group appeared to be irreversible.

In conclusion, we classified the pattern of hypertrophy of LV in patients with AR according to the dimension and the radius to wall thickness ratio and found that there existed good correlation between the pattern of hypertrophy and the function and reversibility of LV dysfunction after AVR. Although LV dimension, mass, pump function at rest normalize in a majority of patients with AR in the late follow up period, some did not show these favourable outcomes. Those patients were noted to have a pattern of hypertrophy with high R/Th, in other words, with high volume/mass ratio or high wall stress caused by insufficient compensated myocardial hypertrophy.

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