Hemodynamic and Angiocardiographic Studies on Cardiodynamics

Experimental Mitral Insufficiency

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SINCE the methods for calculating the left ventricular volume by the use of angiocardiography were introduced,¹⁻¹⁰ detailed studies concerning the volume responses to the various cardiac defects have been performed in many laboratories, which have provided abundant information of diagnostic importance in regard to the quantification of valvular insufficiency, the pressure volume relationship, or the estimation of the stroke work in a variety of cardiac diseases.¹¹⁻²³

More recently, a geometric analysis of the left ventricle has been extended to determining the force acting within and upon the ventricular wall by using Laplace's equation. There have been several studies which were concerned with the anatomic and functional responses to any given pressure or volume load analysed in terms of the force generated in the unit cross sectional area of the left ventricular wall (stress) in addition to the pressure volume relationship.²⁴⁻²⁷ However, no studies have been reported regarding the successive observation on one cardiac defect.

The present studies were undertaken to assess the significance of geometrical changes for modification of the ventricular performance, by means of repeated studies of the same experimental valvular disease with a sufficient time interval.

In addition to that, this report deals with a similar analysis of the left ventricular performance with the infusion of isoproterenol which has a positive inotropic and chronotropic effect on the myocardium, to evaluate the effect of neurohumoral modification of the cardiac function.

METHOD

Fifty-nine hemodynamic observations were made on 28 canine hearts. The dogs weighing 9.5 to 18 kg were anesthetized with sodium pentobarbital 50 mg per kg intravenously. No. 7 Cournand catheter was inserted into the jugular vein and the right heart catheterization was performed by the conventional method. The left ventricle was entered by passing the catheter retrogradely with percutaneous puncture of the femoral artery. The pressure recording system consists of Mingograph and Elma Schonander EMT 34 pressure transducer.

Cardiac output was obtained by the indicator dilution method with the use of the cuvette densitometer, Harvard infusion withdrawal pump, Lexington output computer and Rectigraph (Esterline Anger). Cardiogreen in doses of 10 mg was injected into the superior vena cava, the sampling site being the thoracic aorta.

Angiocardiography

All dogs were suspended in a recumbent position 5.5 cm above the fluoroscopic table by a radiolucent styrol board to equalize magnification factors of both antero-posterior and lateral projection for distortion produced by a tube to film distance. The injection catheter (No. 8 F Cournand angiograph) was placed in the superior vena cava. The red Kifer catheter was indwelled in the left ventricle for pressure recording during exposure. With the aid of Mingograph multichannel recorder, simultaneous recordings

(Received for Publication, December 27, 1969)

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of the left ventricular pressure, electrocardiogram and exposure signs were made, which permitted to relate each frame with the events of the cardiac cycle. One to 1.5 ml/kg of angioconray was injected into the superior vena cava by means of the Gidlund power syringe. Simultaneous antero-posterior and lateral exposures were made at six frames per second during the left ventricular opacification with the use of Elma Schonander film changer.

Left ventricular volume measurement

The left ventricular volume was calculated from the biplane X-ray films by assuming that this chamber could be expressed as an ellipsoid figure as previously described by many authors, and the calculation was based on the formula:

$$\frac{4}{3} \pi \frac{1}{2} \frac{d'}{2} \frac{d''}{2}$$

where l : length of the major axis of the ellipsoid, and d' and d'' : length of the minor axes.

The film to tube distance being adjusted 1 meter for both projections, when the dog was placed so that its heart might be positioned at the same distance from both films, the magnification factor was equal for both projections and this was calculated to be 1.49 in this experiment. Thus the true ventricular volume was calculated as follows:

$$V = \frac{4}{3} \pi \frac{1}{2} \frac{d'}{2} \frac{d''}{2} \frac{1}{1.49^3} = 0.158 l d' d''$$

The long axis was obtained from the lateral film assuming that a length approaching a true spacial length would be projected on this view, and it was determined as the length between the apex and the intersecting point of the aortic root and posterior border of the left ventricle or anterior margin of the left atrium. The perpendicular line was drawn at the mid point to the long axis, and minor axis of the lateral view was determined as a cross diameter. The minor axis of the frontal view was obtained in the same manner, but here the long axis was drawn from the center of the aortic valve to the apex.

Thickness of the left ventricular wall and calculated contractile force in the myocardium

Recently, contractile force in the left ventricular wall has been calculated from the measurements of the pressure and size of the cavity using the Laplace equation, on the assumption that the left ventricle is spherical, and of thin walled

structure. In a thin walled sphere, pressure force against the wall of one half equals the tensile force at the equator separating the two halves of the sphere. This relationship is shown in the following equation:

$$2\pi r w T = \pi r^2 p$$

$$\text{Mural Force (Tension)} = T w = r p / 2$$

$$T = r p / 2 w$$

where T is force per unit cross sectional area of the muscle, w is the wall thickness, r is the radius of the cavity, and p is the transmural pressure. The radius of the cavity and the thickness of the wall were measured on each film of lateral projection. The former was determined as the minor axis in the way above-mentioned, and the latter was obtained by measuring the shortest segment between the outer and inner surfaces of the free wall at the crossing of the radius and the internal surface of the cavity.

In order to analyze changes in the duration of the phases of the ventricular contraction and those in the modes of tension development, the relations of the beginning of the rise of the aortic pressure and the point where the peak stress was attained, to the beginning of the electrical contraction (Q wave in ECG) were studied. The duration of ejection was obtained from the period between the beginning of the rise of the aortic pressure and nadir of dicrotic notch in the aortic pressure. The mean velocity of muscular shortening was approximated from a declivity of the diameter to decrease from the point where it was reduced by 25% of the total change to the point where it diminished by 75%.

Production of the experimental mitral insufficiency

Mitral regurgitation was produced by the method described by MORAIS et al.²⁸ on 13 dogs following the control measurement described above. All dogs were anesthetized with sodium pentobarbital 50 mg/kg intravenously. The ventilation was maintained under a positive pressure breathing by TAKAOKA's respirator through a tracheal intubation. A thoracotomy at the fifth interspace was performed and the pericardium was incised anteriorly parallel to the phrenic nerve. A hook was inserted through the myocardium of the left ventricle and chorda tendinea was torn off with its tip. The degree of regurgitation was determined by the palpable thrill over the left atrium and pulmonary veins, as well as by ballooning out of the left atrial appendage. When

the desired amount of regurgitation had not been produced, additional chordae tendineae were cut in the same manner.

Follow-up studies of chronic experimental insufficiency

Follow-up studies were made in the same manner as the control measurement once or twice on 9 dogs which had survived the attack of the above procedure. The first study was made within a month following the occurrence of mitral regurgitation except in one (No. 15). The second observation was performed at 42nd to 196th day on 5 dogs.

Response to isoproterenol infusion

Hemodynamic alterations associated with isoproterenol infusion were studied in the two groups of dogs. One group consisted of 9 dogs with the intact heart and the other group consisted of 7 dogs with chronic mitral incompetence. After the control measurement of the left ventricular and aortic pressure, cardiac output and angiocardiology, the solution of isoproterenol (0.02 mg/ml) was infused into a foot vein. The rate of infusion was increased slowly and maintained constant when the desired increase of the heart rate had been obtained. In this state the measurement was repeated in the same manner as control.

RESULTS

Of 28 animals, 7 deaths occurred after a control measurement, 5 were due to filariasis, and 2 were caused by hemorrhage. Of 13 dogs operated upon, 3 died of acute pulmonary edema within 24 hours to the 11th day and one died because of inadequate postoperative care. Of 9 dogs in which chronic survival was obtained, data were available only on 5 dogs. These are represented in Table I and Fig. 1. All the failures were referable to the angiocardigraphic difficulties to obtain the exposure at the accurate end-diastolic and end-systolic phase, in spite of the repeated observations.

I. Changes in intracardiac pressure

1. Pulmonary wedge pressure

V wave was not distinguished in each control measurement but clearly visible in 3 of 5 dogs at the first measurement after the onset of mitral incompetence. Two of them showed diminished or decreased V wave at the second observation. The other one revealed the progressive elevation of the regurgitant wave with the progressive increase in the mean pulmonary capillary pressure. This dog had taken a downhill course and died of congestive heart failure on the 96th day. The other 4 dogs exhibited no particular change in the mean value of the pulmonary wedge pressure.

Fig. 1. Changes due to the acute onset of the mitral regurgitation. Three vertical lines in each parameter indicate control study, first and second measurement following the production of the defect, respectively.

Fig.2. Changes in the pressure volume loop following the onset of the mitral incompetence. Solid line shows the control loop, dashed line and chain line illustrate the diagram at the first and second measurement after the regurgitation had occurred. The mitral incompetence gave rise to the loss of the isometric contraction, rightward shift of the loop and an increase in the enclosed area within the loop.

2. Pulmonary arterial and right ventricular pressure

There was no particular change in the pulmonary arterial pressure. The right ventricular

pressure also remained unchanged.

3. Left ventricular pressure

The left ventricular systolic and diastolic pressure were not markedly changed. However, the end-diastolic pressure increased in all dogs at the first measurement after the mitral regurgitation had occurred, 4 to 18 mmHg on the average. At the second observation, 2 of them were shown to be decreased, 2 remained the same as the previous value, and the other one showed further increase.

4. Aortic pressure

Experimentally developed mitral incompetence brought about no particular change in the aortic pressure.

II. Heart rate

The heart rate was variable between 123 to 189 per minute, and there was no constant change due to mitral incompetence.

III. Cardiac output and effective stroke volume

Cardiac output of control ranged between 1.94 to 3.24 L/min averaging 2.59 L/min which

Fig.3. Instantaneous values of the tension (dashed line), stress (solid line), intracavitary pressure (chain line), circumference (middle curve) and the thickness of the free wall (lower curve) were plotted against time expressed in fractions of a second after the R wave of the electrocardiogram. In the early stage, the distension of the ventricular wall was evidenced by the elevated stress with augmented size of the cavity, reduced wall thickness and unchanged intracavitary pressure. With a sufficient time interval, the muscular hypertrophy was recognized by the re-elevated wall thickness and the decrement of the initially elevated wall stress. The mural tension continued increasing with the augmented external work.

TABLE I HEMODYNAMIC CHANGES FOLLOWING THE ONSET OF MITRAL INSUFFICIENCY

No. days	PC		PA		RV		LV		Ao		HR/m	Dye		Angio		Ej. Fr. %	Regurg. Vol. ml		SW gmcn
	v	m	s	d	m	s	d	ed	s	d		CO L/m	SV ml	EDV ml	ESV ml				
c	7	40	17	25		40	-1	2	160	-6	4	2.00	16	41	21	20	49		3624
15	67	7	35	13	20	27	3	4	155	-10	23	1.74	12	55	27	28	50	16	4304
196		4	35	21	27	33	0	3	160	0	13	2.13	13	60	25	35	53	23	6154
c	0	19	11	13		19	-2	0	164	2	4	1.94	11	25	13	12	50		2326
16	44	13	5	25	15	30	3	5	175	4	14	1.54	9	44	19	25	57	16	4869
193		5	3	25	15	25	-1	3	160	4	14	1.64	10	44	18	26	59	16	60
c	7	30	11	19		32	0	1	140	3	4	3.52	19	40	18	22	55		3373
18	24	15	2	28	15	30	0	5	148	3	16	1.87	12	62	30	32	52	20	4379
135		9	30	18	22	30	-5	1	160	4	12	2.85	17	92	40	52	56	35	7820
c	4	37	12	21		42	-6	2	146	0	2	2.21	12	23	9	14	61		2536
19	16	4	22	14	17	22	-3	1	132	0	12	1.81	11	34	12	22	64	10	46
96		6	21	11	15	21	-4	0	140	0	14	2.11	12						
c	3	23	8	15		23	0	2	182	0	4	3.24	21	32	12	20	63		4164
23	23	14	30	20	25	32	-2	1	160	0	26	1.50	9	56	17	39	69	30	77
42		35	21	35	23	37	0	2	160	2	26	2.06	11						7126

PC=pulmonary capillary pressure (mmHg), PA=pulmonary arterial pressure (mmHg), RV=right ventricular pressure (mmHg)

LV=left ventricular pressure (mmHg), Ao=aortic pressure (mmHg)

v=v wave, m=mean, s=systolic, d=diastolic, ed=end diastolic, HR=heart rate, Co=cardiac output, SV=stroke volume,

EDV=end diastolic volume, ESV=end systolic volume, Ej. Fr.=ejection fraction, Regurg. Vol.=regurgitant volume

SW=stroke work

TABLE II CHANGES IN WALL THICKNESS, RELATIVE WALL THICKNESS, STRESS, RATE OF CIRCUMFERENTIAL SHORTENING FOLLOWING THE ONSET OF

Dog No.	days after op.	Press mmHg	End diastolic			R.W.T.	End systolic			Stress	
			Vol. ml	W.T. cm	D cm		Vol. ml	W.T. cm	D cm	In $\times 10^3$ dynes/cm ²	Pk
15	c	4	41	1.06	5.05	0.21	21	1.56	3.70	13	471
	67	23	55	1.10	5.75	0.19	27	1.60	4.10	84	413
	196	13	60	1.11	5.90	0.19	25	1.50	4.10	47	473
16	c	4	25	1.00	4.40	0.23	13	1.50	3.13	12	353
	44	14	44	0.90	5.50	0.16	19	1.41	3.70	57	428
18	c	4	40	1.20	4.80	0.25	18	1.92	3.30	11	281
	24	16	62	0.80	5.75	0.14	30	1.60	4.30	77	508
	135	12	92	1.20	7.00	0.17	40	1.90	4.90	47	377
19	c	4	23	0.90	4.65	0.19	9	1.38	3.20	13	493
	16	12	34	0.90	5.25	0.17	12	1.50	3.20	47	368
23	c	4	32	1.14	4.45	0.26	12	1.65	3.20	11	360
	23	26	56	1.01	5.80	0.17	17	1.62	3.40	100	411

W.T.=wall thickness, D=diameter, R.W.T.=relative wall thickness, In=initial stress, Pk=peak Q-Ej=interval between Q and the beginning of the ejection, Ej. Pd=ejection period, dl/dt=mean

decreased in all at the first measurement following the production of the defect, to the range of 1.50 to 1.87 L/min with the value of 1.69 L/min (-29%) on the average. With further observations, all animals showed a moderate regain of its value. The changes in the effective stroke volume were on the same direction as cardiac output.

IV. Left ventricular volume

The changes in the left ventricular volume following the occurrence of mitral incompetence were characterized by the increase in both the end-diastolic and end-systolic volume, which resulted in an augmentation of the total stroke volume. The ratio of an increase in the end-diastolic, end-systolic volume and total stroke volume averaged +63% (from 32 to 52 ml), +40% (from 15 to 21 ml) and +62% (from 18 to 29 ml) respectively. In 3 dogs on which the second measurement was possible, 2 showed further increase in end-diastolic volume with less change in end-systolic volume, and the other represented no further volume change.

Ejection fraction estimated as a ratio of the total stroke volume to the end-diastolic volume was brought on a minimal increase in 4 dogs and a slight decrease in one. There was no striking change at the second observation. It remained

almost unchanged on the average, 56% in control and 58% after the onset of mitral regurgitation.

Regurgitant volume was calculated from the discrepancy of total and effective stroke volume. The ratio of a regurgitant volume to the total stroke volume, being expressed as a regurgitant percent, proved to be 46 to 77% in these experiments. Of the 3 dogs on which the measurement was tried twice after a chordal rupture, 2 showed further augmentation of regurgitant volume with an increment of regurgitant percent, and the other one remained almost the same as the previous value.

V. Pressure volume diagrams

The left ventricular pressure and volume were related at corresponding times in the whole cardiac cycle to obtain a pressure volume diagram. The representative is illustrated in Fig. 2. In control, isometric contraction was characterized by a sharp rise in pressure with little change in volume followed by a ventricular ejection with little change in pressure. There was a rapid fall in pressure with little volume change in isometric relaxation. The ventricular expansion was associated with little change in pressure. When mitral regurgitation had occurred, both the end-diastolic and end-systolic volume were enlarged with the

EJECTION PERIOD AND THE
MITRAL INSUFFICIENCY

<i>R-Pk</i> sec.	<i>Q-Ej</i> sec.	<i>Ej.Pd</i> sec.	<i>dl/dt</i> mm/sec.
0.09	0.12	0.18	107
0.075	0.09	0.20	91
0.08	0.08	0.17	86
0.09	0.13	0.13	92
0.08	0.10	0.17	100
0.08	0.11	0.12	164
0.05	0.11	0.15	81
0.07	0.11	0.15	147
0.07	0.09	0.14	158
0.06	0.08	0.16	118
0.08	0.10	0.15	118
0.06	0.08	0.15	166

stress, *R-Pk*=*R* to peak stress interval
rate of circumferential shortening.

enhanced total stroke volume. There was a marked change in the configuration of the pressure volume loop, compared with that of normal. A valvular incompetence led to a slower rise of pressure as soon as the volume began to decrease. The net left ventricular stroke work was calculated by the planimetric integration of the area enclosed within the pressure volume loop. In each measurement, this had been significantly augmented in consequence of the onset of mitral regurgitation.

VI. Wall thickness and calculated contractile force in the myocardium

The results of these calculations are listed in Table II. In control, the thickness of the free wall of the left ventricle averaged 1.06 cm at the end diastole, while it decreased to 0.94 cm at the first measurement following the onset of mitral regurgitation.

The ratio of the wall thickness to the diameter of the cavity was shown to be decreased uniformly, which ranged between 0.19 and 0.26, averaging 0.23 in control, while it averaged 0.16 ranging from 0.14 to 0.19 in those with regurgitation. Consequently, the calculated initial stress was markedly enhanced with the occurrence of mitral incompetence in all animals. However, in 3 dogs

on which the second postoperative study was performed, the wall thickness was shown to be augmented with the further increase in the diameter of the cavity and the lowered end-diastolic pressure resulting in a decrease in the initial stress.

Instantaneous changes in stress and tension were plotted against time at 0.01 sec intervals in each measurement. Representative is shown in Fig. 3. Changes in the absolute value of the peak stress were not conclusive but the stress and tension during contraction reached the maximum level earlier in those with mitral incompetence. The high peak stress showed a tendency to decline rapidly but there was no distinct and uniform difference in the configuration of the stress curve associated with the production of the defect. The duration of the ejection period, though being influenced by the heart rate, represented the tendency to be prolonged.

The roughly approximated mean velocity of muscular shortening was not influenced in the consistent fashion.

VII. Response to isoproterenol

The data obtained in this study are summarized in Table III and Figs. 4 and 5.

1. In normal group

Isoproterenol infusion resulted in an increase in the heart rate in all. It averaged 171 in control while 236 during the drug infusion (+38%). The left ventricular end-diastolic pressure fell. All animals had an increase in cardiac output whereas the stroke volume generally remained unchanged. There was a 58 percent increase in cardiac output over control values on the average, (The mean cardiac output of 3.00 L/min in control to 4.60 L/min during infusion). Both the left ventricular end-diastolic and systolic volumes were decreased in the same amount, from 30 to 23 ml and from 11 to 3 ml on the average, respectively. Consequently, the pressure volume loop was shifted leftward as shown in Fig. 6 and the ejection fraction resulted in a proportionate increase.

Mural forces expressed as stress were markedly decreased in the whole cardiac cycle as shown in Fig. 8 (A). The initial stress averaged 21×10^3 dynes/cm² in control which decreased to 8×10^3 dynes/cm² with the drug, and the peak stress diminished from 414×10^3 to 253×10^3 dynes/cm² on the average. The peak stress was attained earlier and the velocity of muscular shortening was invariably enhanced.

TABLE III RESPONSE TO ISOPROTERENOL

dog No.	HR	LV s d ed mmHg	Ao s d mmHg	Dye CO SV L/m ml	Angio EDV SV ml	Ej. Fr. %	Regurg. Vol ml	SW g/mcm	Stress In. Pk $\times 10^3$ dynes/cm ²	Q-Ej sec	dl/dt mm/sec
<i>Normal group</i>											
21 C	164	158 4 9	162 122 140	3.43 21	36 12 24	67		4583	33 443	0.07	85
I	226	160 6 3	160 110 126	5.51 24	27 4 23	85		4026	9 312	0.05	240
23 C	156	180 0 4	184 156 172	3.24 21	32 12 20	63		4114	11 360	0.08	118
I	240	134 0 2	144 118 132	5.80 24	25 3 22	88		3454	5 152	0.05	295
25 C	197	158 2 7	154 122 138	3.14 17	27 10 17	63		3074	29 519	0.07	145
I	255	142 0 3	156 118 138	4.42 17	21 3 18	86		2897	7 268	0.04	406
27 C	162	156 0 7	138 110 122	2.83 17	28 11 17	61		2899	21 408	0.08	107
I	220	150 -2 4	144 92 122	3.50 16	21 3 18	86		2713	12 271	0.05	289
28 C	175	140 0 4	135 104 120	2.35 14	26 12 14	53		2243	13 344	0.09	133
I	240	142 0 2	154 100 120	3.76 15	21 4 16	76		2802	6 263	0.05	474
<i>MI group</i>											
15 C	164	160 0 13	160 130 152	2.00 12	60 25 35	53	23 66	6154	47 473	0.08	86
I	194	130 3 4	140 70 107	3.94 17	43 4 39	91	22 56	5093	15 150	0.05	433
16 C	164	160 4 14	164 130 144	1.64 10	44 18 26	59	16 60	4304	57 428	0.08	100
I	200	150 0 2	164 120 138	3.84 19	31 5 26	84	7 27	3726	9 200	0.06	463
18 C	171	160 4 12	152 126 138	2.85 17	92 40 52	57	35 67	7820	47 377	0.07	147
I	200	150 0 6	158 116 136	5.46 27	77 23 54	70	27 50	7752	13 232	0.06	255
19 C	167	140 0 14	140 118 134	1.81 11	34 12 22	64	10 46	3250	47 368	0.06	118
I	250	150 0 10	152 108 132	4.68 19	32 5 27	84	8 30	4746	16 225	0.05	409
23 C	174	160 0 26	154 132 146	1.50 9	56 17 39	69	30 77	7126	100 411	0.06	166
I	214	160 4 10	176 128 152	4.13 15	43 10 33	77	18 55	6562	29 360	0.05	240
C: control I: with Isoproterenol infusion

Fig.4. The effect of isoproterenol on the normal heart. The left vertical line of each parameter shows the control value and the right line the value during the drug infusion.

HR is heart rate, EDV is end-diastolic volume, ESV is end-systolic volume, CO is cardiac output, SV is stroke volume, SW is stroke work, EDP is end-diastolic pressure, and Ej, Fr. is ejection fraction.

Fig.5. The effect of isoproterenol on the heart with mitral incompetence. Note the same directional change as in the normal heart. Though the changes in the total stroke volume were insignificant, the effective stroke volume was markedly elevated by the drug with suppression of the regurgitation.

EFF. SV is effective stroke volume, TOT. SV is total stroke volume, and Reg.% is regurgitant percent.

2. In dogs with chronic experimental mitral insufficiency

An equivocal response was noted in those with mitral incompetence as seen in the normal

group. The heart rate increased by 26% on the average. The drug infusion produced consistently the same directional change in cardiac output and in the left ventricular end-diastolic pressure,

Fig. 6. Effect of isoproterenol on the pressure volume loop of the normal heart. The solid line illustrates the control loop and the dashed line the loop after the drug. The infusion of the drug made the loop shift leftward with the diminished end-diastolic pressure. Stroke work was not meaningfully altered.

but the ratios of the changes were unproportionately large, compared with those of the normal group. The initially elevated end diastolic pressure (averaging 16 mmHg, ranging from 12 to 26 mmHg) was markedly decreased to almost the normal value (with an average of 6 mmHg (-59%) ranging from 2 to 10 mmHg). A prominent rise in the initially decreased cardiac output was observed. The mean cardiac output before iso-

Fig. 7. Effect of isoproterenol on the diseased heart. The response was almost the same as that of normal heart.

proterenol infusion was 1.96 L/min with a range of 1.05 to 2.00 L/min and the mean cardiac output after the drug was 4.41 L/min (+125%) ranging from 3.84 to 5.46 L/min. The effective stroke volume obtained from the dye dilution method was also seen to be augmented by 58%. The mean effective stroke volume was 12 ml in control and 19 ml during the drug infusion. On the other hand, the changes in the total stroke volume calculated from angiocardigraphy were less, averaging 35 ml in control and 36 ml with isoproterenol. Consequently, the regurgitant volume and the regurgitant percent decreased significantly in all dogs, 23 ml to 16 ml, and 64% to 44% on the average, respectively. Both the end-

Fig. 8. Instantaneous values of stress, circumference and thickness of the wall were plotted against time expressed in fractions of a second after the R wave of the electrocardiogram. The equivocal changes are noted in both normal (A) and diseased conditions (B). Isoproterenol brought about a decrease in the stress, an enhancement of muscular shortening and the augmentation of wall thickness. The peak stress was attained earlier with the drug.

Fig. 9. Serial observation of the heart subjected to the mitral regurgitation. Lateral view was presented to show the gradual increase of the left atrial cavity size with the gradual enlargement of the left ventricular volume following the onset of mitral regurgitation.

diastolic and end-systolic volumes were decreased in the same manner as the normal group resulting in an elevation of the ejection fraction. The alteration in the stroke work was not statistically significant. Isoproterenol brought about almost the same change on the stress curve, time course of circumferential shortening and an instantaneous changes of the left ventricular wall thickness as seen in the normal group except that the initial stress was more elevated (60×10^3 dynes/cm²) before the infusion and decreased more markedly (16×10^3 dynes/cm²) by the drug. The decrease in the peak stress (from 411×10^3 to 233×10^3 dynes/cm²) and the increase in velocity of the muscular shortening (from 37 to 113 mm/sec) were almost as the same with those noted in the normal group.

The shortening of the time interval between the beginning of the electrical contraction and the peak stress was less marked, for the mitral incompetence had already shortened this period considerably. One representative of these changes is illustrated in Figure 7 and 8-(B).

DISCUSSION

I. Data from the right heart catheterization

There have been abundant demonstrations concerning the hemodynamic feature of the acute mitral insufficiency resulting from the rupture of either a papillary muscle or chordae taendineae²⁹⁻³³. A marked elevation of the mean left atrial or pulmonary wedge pressure with a distinct V wave is the most prominent feature in these conditions. However, these findings form a striking contrast with the data obtained in the present studies where changes in the pulmonary wedge pressure were less dominant in all but one which had the maximum regurgitation in our series and died of heart failure.

On the other hand, attention has been focussed on a group of patients with severe mitral regurgitation in whom the elevation of the left atrial pressure was not evident and the change in a compliance of the atrial wall has been suggested to be most responsible for the normal pressure existing in the greatly enlarged left atrium.³⁴⁻³⁵

In the present experiments, though a calcula-

Fig.10. Total stroke volume and stroke work were plotted against the end-diastolic volume. As a consequence of the volume overload total stroke volume and stroke work were increased proportionately to the enlargement of the end-diastolic volume, but higher correlation was found in the former relationship.

tion of the left atrial volume was not carried out because of the difficulty in demarcating the accurate left atrial border as the beginning of exposure was adjusted to the subsequent left ventricular opacification, the enlargement of the left atrium was definitely recognized in some as shown in Fig. 9. This fact would suggest that the rapid enlargement of the left atrium without a decrease in a compliance of the wall as well as an elastic pulmonary vein was responsible for the dumping of the elevation of the pressure due to volume overload.

Consequently, the pulmonary artery and the right side of the heart remained unaffected by the defect in the mitral valve.

II. Data from the left heart catheterization and calculated ventricular volume

The changes brought about in the left side of the heart were characterized by a marked elevation of the left ventricular end-diastolic pressure and the enlargement of the left ventricular cavity.

The end-diastolic pressure has been a method for the assessment of a functional state of the ventricle and the failing ventricle has been characterized by the elevation of the end-diastolic pressure.³⁶⁻⁴² According to many published reports,

the rise of the left ventricular end-diastolic pressure is a prominent feature in acute mitral insufficiency,²⁹⁻³³ but this change is not distinct in the long standing mitral incompetence caused by a valvular involvement of the rheumatic process.^{35,43} In the present studies, it was shown that the acute onset of mitral regurgitation had been accompanied by a rise of the left ventricular end-diastolic pressure as well as increase in the cavity volume in all dogs. However, at the second observation the changes in the end-diastolic pressure were not always directed to the same direction as changes in the end-diastolic volume. These findings offer another support to the concept that an enlargement of the left ventricular volume may assume responsibility for the elevation of the end-diastolic pressure in the case of the acute volume overload, where the elevated end-diastolic pressure is supposed to reflect a diminished ventricular compliance, but the increased left ventricular volume can not necessarily be a fundamental determinant of the left ventricular end-diastolic pressure.⁴⁴

Close correlations between the total stroke volume and the left ventricular end-diastolic volume are shown in Fig. 10. This relationship undoubtedly satisfies a fundamental property of the ventricular muscle, operated by the Starling's law of the heart in which the force of contraction is a function of the length of the muscle fiber.

In the past, when the determination of the ventricular volume was not available, atrial pressure or ventricular end-diastolic pressure was related to the systolic pressure, the stroke volume or the stroke work to explain the essential law of the heart only indirectly.^{39-42,70} Owing to the development of the volumetric angiocardigraphy which has proved to be the most accurate method to obtain the left ventricular end-diastolic volume,^{45,46} the most direct and relevant evaluation of this principal mechanism has become possible in the beating in situ heart.⁴⁷

Though Starling's law was derived originally from the experiment on the heart lung preparation deprived of all nervous connections, and in a beating heart, the energy release during myocardial contraction depends not only on the mechanical factor but also on the neurohumoral one, the law remains unquestionably operative under all conditions and it can be said that the Starling's mechanism was identified as a dominant one in the control of the left ventricular contraction when the heart was subjected to the acute volume overload.

III. Left ventricular mural force during contraction

The previous works of many investigators have indicated that total energy expended by the heart during contraction is a sum of energy utilized during the dynamic work to move the blood and that consumed in the static work as a compression pump.^{48,69} The former is expressed as a pressure volume work ($\int p dV$) and the latter as the tension time integral ($\int T dt$). Determination of the tension has been the subject of intensive interest and investigation.^{48,69,71,72} It was shown that the Laplace equation applied to the heart as early as 1892.⁷¹ However, it was not until quite recently when the development of the angiocardiology had made it possible to visualize the radii of curvature and the thickness of the left ventricular wall, that this equation has been brought into wide use for the indirect estimation of the stress and the tension generated in the ventricular wall.²⁴⁻²⁷ The Laplace equation is applicable primarily to a thin walled sphere but the ventricle can not be a thin walled structure and the cavity is irregularly shaped and mural forces can no longer be distributed evenly throughout the wall during systole. However, HEFNER⁴⁹ and COTHRAN⁵⁰ demonstrated the high degree of correlation between the calculated left ventricular force and directly recorded one and SANDLER et al. reported that the calculation of stress with the above equation underestimated the actual peak stress by 30 to 40% only when the ventricular wall thickness might equal or exceed its associated radii.²⁴ These evidences emphasize that the equation holds true in the estimation of the mean of forces across the ventricular wall.

The structural changes of the free wall can not be evaluated precisely even in the serial observation of the same animal. For the variation in the X-ray distortion is considerably varied among the enlarged ventricle. So these changes were analysed in the form of the relative wall thickness in order to make the variation in distortion among the different sized chambers relatively small. The acute onset of volume overload brought the decrement in the relative wall thickness and the increment in the initial wall stress, and peak stress was attained earlier but the configuration of the stress curve was not altered significantly in those with mitral incompetence. The tendency for the greater peak stress toward the rapid decline was observed equally both in normal ventricle and those with mitral defect. These findings are con-

trasted with the observations of GAULT et al. that in the heart with myocardial disorder, the rate of stress development was less than that of normal heart, and relatively high stress was sustained throughout most of systole.²⁷ With due regard to their view, it seems to be probable that the myocardium has remained unaffected by the enlargement of the ventricle and the mechanical adaptation should have taken place without the change in the intrinsic property of the cardiac muscle.

Further evidence for the intact myocardial function has been provided by the unchanged ejection fraction. It has been widely accepted that the ejection fraction is decreased in myocardial diseases, while the increased value represents a more forceful contraction ascribed to the pressure overload or to the inotropic stimulation.^{11-14,18,19,22}

Following the onset of mitral regurgitation the blood was propelled sooner into the aorta after the beginning of the ventricular contraction, as a consequence of the earlier attainment of the maximum active state which permits the ventricular pressure to arrive earlier to the sufficient level for the opening of the aortic valve.

In addition to this shortening of isometric contraction which can be attributed to a reduction of the resistance against which ventricular force is exerted,⁶⁴ the increased end-diastolic fiber length due to cardiac dilatation is responsible for the prolongation of mechanical systole.⁶⁸ And prolonged duration of systole and cardiac dilatation enhance the stroke volume on the one hand, but cause the increment in the time tension integral ($\int T dt$) on the other.

IV. Development of cardiac hypertrophy

Following the initial catastrophic events, muscular hypertrophy was evidenced by a significant regain of the relative wall thickness at end-diastole, with repairment of the initial stress. Physiologic aspects of cardiac hypertrophy have been discussed repeatedly^{25,51-57} but the opinions are not conclusive concerning the biological importance of this fundamental pathologic change in cardiovascular disease. The major controversy consists in its useful adaptive mechanism and its deleterious effect. GRANT adduced the following examples in evidence of the deleterious effect of cardiac hypertrophy; i.e. 1) experimentally no meaningful increment of the reserve capacity for work was noted in the hypertrophied heart, 2) electrocardiographic changes in ST-T component

in cases of marked ventricular hypertrophy suggest a condition of chronic coronary insufficiency, 3) there are some clinical cases of heart failure which have apparently been caused by a muscular hypertrophy, 4) in some rare instances where the work of the heart was increased suddenly by a cardiac accident, patients took universally a downhill course without being influenced by the gradual development of hypertrophy.⁵³

On the other hand, cardiac hypertrophy is looked upon as a natural consequence of the increased work of the heart and various hypotheses have been postulated concerning the nature of the stimulus to the hypertrophy. Among those which BADEER cited, there are 1) nutritional deficiency, 2) hormonal unbalance, 3) increased mechanical work of the myocardium, 4) myocardial dilatation, and 5) the increased myocardial metabolic rate per beat.⁵⁴

Although various factors may play an important stimulating role in the development of cardiac hypertrophy each in its own way in each cardiac defect, consideration was given to the possibility that the distension of the myocardial fiber could be a most important determinant of the hypertrophic process in the circumstances prepared in the present experiments. The typical course of development of the hypertrophy is shown in Fig. 3. At the onset of regurgitation, the diastolic overload had been met by an increase in the cavity volume leading to a distension of the wall, which brought about fundamental changes in the elastic property of the myocardium resulting in an elevation of contractile tension and stress both to initiate and to maintain the contraction. In spite of the considerable increase in the total stroke volume which is a function of the elevated end-diastolic volume, the effective stroke volume was markedly limited for the greater facility of the reflux through the mitral valve. When the backward resistance can no longer be enhanced, an adequate forward flow can only be provided by an increase in the total stroke volume. In the face of these conditions the left ventricular volume had kept on increasing to be associated with the further elevation of stress and tension. Here the left ventricular wall is supposed to have thickened in order to restore this elevated stress to normal. Consequently, when sufficient time had elapsed, a considerable amount of the effective stroke volume was maintained by the increased total stroke volume where the increment of the external work was operated at the expense of the static work with the relatively less change

in the wall stress.

These findings are in accordance with those of SANDLER et al. who suggested that hypertrophy is a primary adaptive mechanism that increases the mural force of contraction by increasing the thickness of the wall with tendency to maintain the stress within a certain limit.²⁴

In the dogs which died of heart failure, it is likely that the myocardial segment had been stretched in length beyond the limit only to be followed by a decline in stress and tension, and the static work could no longer meet the increased dynamic work.

V. Response to isoproterenol

Isoproterenol, which is primarily a vasodilator by stimulating a beta adrenergic receptor, has also the direct inotropic action on cardiac performance. The results of the present experiments are consistent closely with those reported in the literature as regards the increase in the heart rate and cardiac output. The potency of this drug in its effect on the rate of cardiac beat has widely been accepted. The receptor mechanism in producing this change has been suggested to be different from those involved in producing the change in inotropy of the myocardial fiber. This receptor is supposed to be in higher centers and nodal tissues.⁵⁸⁻⁶⁰ In most of the previous investigations, the augmentation of cardiac output has been regarded as the result of the increase in the heart rate in association with the elevation of the stroke volume.⁶¹⁻⁶³ The results presented in this communication indicated that the total stroke volume was not essentially altered following the adaptation of isoproterenol either in the normal or the mitral-incompetent heart, however the effective stroke volume was considerably augmented in the latter group resulting in a suppression of the regurgitation. And the following factors are supposed to stand in a causal relation to the reduction in the regurgitation: 1) the reduced forward resistance owing to the intrinsic effect of the drug as a vasodilator, 2) the diminished regurgitant orifice on account of the decreased chamber volume and of the enhanced contraction of the muscular portion of annular margin.⁶⁷ 3) the reduced time of deformation of ventricular fluid mass in consequence of the increased celerity of the ventricular contraction.⁶⁵

The other hemodynamic responses were shown to be of the same direction both in normal and in mitral incompetent groups.

These changes were represented as a reduction

in the preload and an increase in inotropism for the ventricular contraction. The former effect is evidenced by the decrease in pressure and volume at the end-diastole. This has been accounted for as a result of a redistribution of the blood away from the central reservoir, the decrease in the central venous tone and the increase in the atrial and ventricular distensibility.^{6,1} According to the present observation, an effect of the distensibility of the left ventricle seems to be the most adequate explanation for this decrease in the left ventricular end-diastolic pressure, for the end-diastolic volume was reduced according to the abbreviation of the diastolic filling period proportionately to the increased heart rate simply being associated with an increase in the left ventricular wall thickness at the end-diastole which resulted in a decrease in the initial stress. The smaller chamber has the geometrical disadvantage that the stroke volume is less than that of the larger chamber at the same muscle shortening and contractile force is decreased as long as the cardiac muscle is operated under the Frank Starling's mechanism. Under these circumstances more rapid and more complete muscle shortening is required to maintain the stroke volume unchanged. The observed effect of isoproterenol on muscle shortening is in accordance with the direct inotropic effect on the contractile element, and these changes are substantially associated with the decrease in the afterload against which the heart contracts.

And mural force (stress) to maintain the same intracavitary pressure as that of control was seen to be reduced markedly with the infusion of isoproterenol as a result of a decrease in the size of the cavity and a corresponding increment of the wall thickness. According to the present experiments, a positive inotropic intervention with isoproterenol is characterized by the fact that more rapid velocity of contraction and greater extent of shortening were attained by the contraction which originating from the smaller end-diastolic volume with the smaller mural force.

It is evident that the cardiac performance can be modified essentially by the two major factors, i.e. mechanical and neurohumoral. The importance of the end-diastolic volume as one of the mechanical factors which determine the regulation of the cardiac performance was shown in the hearts subjected to the acute volume overload. On the other hand, an alteration of inotropy of the myocardial fiber was shown to depend primarily of the effect of catecholamins. And these

two factors must carefully be analysed for the detailed evaluation of the disease process of cardiac defects.

SUMMARY

Mitral regurgitation was produced in experimental dogs by cutting the chorda tendinea. The biplane angiography was applied to follow up the geometrical response of the left ventricle to the increased volume overload. The left ventricular cavity volume had continued increasing since the onset of cardiac defects to make up for the diminished effective stroke volume by increasing the total stroke volume which had been achieved without any significant change in the ejection fraction. The end-diastolic pressure which had been elevated soon after the beginning of mitral regurgitation, was shown to be reduced after a sufficient time had elapsed as a consequence of the increased compliance of the left ventricular wall with the development of a muscular hypertrophy. The hypertrophy was evidenced by the regain in the thickness of the left ventricular wall, and the initial stress was shown to be decreased in consequence. The peak stress was not changed in any consistent fashion but it revealed the tendency to be more elevated when the distension was more marked. These observation suggested that the distension of the ventricular wall should be the primary stimulus for cardiac hypertrophy.

The inotropic intervention of the cardiac performance was almost the same in both the normal and diseased hearts. The more rapid velocity of contraction and greater extent of shortening was attained by the contraction originating from the smaller end-diastolic volume with the smaller mural force. These findings form a striking contrast with those observed following the rupture of chorda tendinea and it was indicated that the regulation of the cardiac function following the onset of the acute volume overload depended primarily on the mechanical factor rather than neurohumoral. The augmentation of cardiac output was attained by the increase in the heart rate with an almost unchanged stroke volume. In those with mitral incompetence, the regurgitation was significantly suppressed by isoproterenol. These data suggest the clinical usefulness of this drug in the treatment of acute heart failure due to mitral regurgitation.

Acknowledgement

The writers wish to express their thanks to Prof. M.

Takayasu, Dr. Y. Nohara and staff of the cardiac catheterization laboratory of Kyoto university for their active interest and helpful discussion, to Dr. S. Kawakita for his constant encouragement, and to the members of the department of radiology of Tenri hospital for their generous collaboration.

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