Effect of Propranolol on Left Ventricular Work in Aortic Stenosis

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The reduction in myocardial contractility produced by beta-adrenergic blockade may have a useful therapeutic action in some disease states, such as angina pectoris and hypertrophic obstructive cardiomyopathy, but this treatment can have adverse effects when myocardial contractility is seriously impaired. Interference with myocardial contraction may be evident as a reduction in the rate of rise of ventricular systolic pressure or in the rate of emptying of the chamber, and changes in ventricular diastolic pressure may follow. However, full appreciation of the changes in myocardial performance requires measurement of the diastolic volume of the ventricle.

We have been using the measurement of left ventricular volume by the thermodilution method in our assessment of patients with severe aortic stenosis as a preliminary to aortic valve replacement, and we have also been producing beta-adrenergic blockade with propranolol in these patients in an attempt to distinguish a relatively healthy left ventricular muscle that can function satisfactorily in the absence of sympathetic nervous activity from one in which sympathetic drive is needed to maintain satisfactory performance. These investigations have enabled us to study the effect of propranolol on left ventricular work in patients with aortic stenosis.

SUBJECTS AND METHODS

Six patients were studied. All were thought, on clinical grounds, to have severe calcific aortic stenosis and had serious symptoms (Table I). Some aortic incompetence was present in 5 patients, but was only of slight or moderate degree. The electrocardiogram usually showed left ventricular hypertrophy, but in two patients there was also evidence of myocardial damage.

Cardiac catheterization was performed after premedication with promethazine 50 mg., intramuscularly. Catheterization of the right heart and measurement of the cardiac output by the Fick principle was performed via the right saphenous vein using a Cournand catheter. Blood gases were analysed by the van Slyke method and pressures were referred to a baseline at the sternal angle. The catheter was then replaced by a Brockenbrough catheter and the left ventricle was entered by transseptal puncture. A short length of polyethylene tubing (PE 120) was placed in the right femoral artery by the percutaneous method, and cardiac output was measured by the indicator dilution technique using a Gilford cuvette and indocyanine green. The indicator dilution curve was calibrated by the dynamic method (Emanuel *et al.*, 1966). The polyethylene tube was then replaced by a No. 5 teflon Gensini catheter which was passed to the ascending aorta about 1 cm. above the aortic valve. The aortic pressure gradient and left ventricular diastolic pressure were measured with a P 23 G Statham strain gauge and a N.E.P. photographic recorder at a paper speed of 80 mm./sec. A nickel-chromium to nickel-aluminium thermocouple wire with a time-constant of 0·1 sec. (Watson, Fleming, and Hamer, in preparation) was inserted into the aortic catheter until it just protruded from the tip. Multiple thermodilution curves were recorded on the photographic recorder after the injection of 5 to 10 ml. of ice-cold saline into the left ventricle (Fig. 1). Injections were repeated as soon as the curve reached the baseline. The patient was then given 5 mg. propranolol slowly into the left ventricle. After 10 minutes the thermodilution curves were repeated. Next the thermocouple was withdrawn and the pressure measurements were repeated. Finally the arterial catheter was replaced by the polyethylene tube and the cardiac output was measured again by the indicator dilution method.

The thermodilution curves and the measurements of cardiac output by indicator dilution were performed within a ten-minute period without evident change in the state of the patient. The stroke volume was calculated from the cardiac output and heart rate. The

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TABLE I
CLINICAL ASSESSMENT AND CATHETERIZATION FINDINGS

Patient	Age (yr.)	Symptoms			Degree of aortic in-competence (0–4)	Electrocardiogram	B.S.A. (m.²)	Cardiac output* (l./min.)	Aortic valve area (cm.²)
		Dyspnœa	Angina	Syncope					
E.L.	51	+			0	Left ventricular hypertrophy	1·97	6·1	0·6
E.O.	52	+	+	+	2	Left ventricular hypertrophy	2·02	6·2	0·6
F.H.	48	+	·		2	Left ventricular hypertrophy and ischæmia	1·58	4·0	0·6
H.B.	61		+	+	2	Left ventricular hypertrophy and old infarct	1·78	5·6	0·5
J.W.	57	+	+		1	Normal	1·85	5·8	0·7
C.P.	52	+			1	Left ventricular hypertrophy	1·81	5·1	0·5

* By Fick principle.

ratio between the steps of the thermodilution curve (Fig. 1) was measured, beginning from the fourth beat after the appearance of the indicator and continuing until accurate measurement became difficult. If an ec-topic beat occurred no measurements were made until there had been two subsequent normal beats. Up to five measurements were made on each curve. From 2 to 8 curves were obtained before and after propranolol
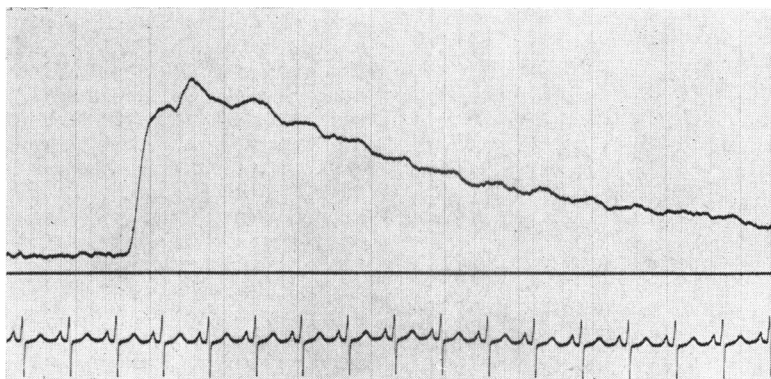

FIG. 1A. Thermodilution curve from the present study showing little change between successive heart beats, indicating a large left ventricular volume.

Fig. 1B. Thermodilution curve from a patient with less severe aortic stenosis showing a large change in temperature from beat to beat, indicating a small left ventricular volume.

TABLE II

HÆMODYNAMIC MEASUREMENTS
BEFORE AND AFTER PROPRANOLOL

Patient		Left ventricle systolic pressure (mm. Hg)	LV diastolic pressure (mm. Hg)		Cardiac output* (l./min.)	Heart rate (per min.)	Stroke volume (ml.)	LV end-diastolic volume (ml.)
			z	a				
E.L.	Before	220	7	15	5·6	66	85	405
	After	220	10	20	4·9	56	88	435
E.O.	Before	190	18	33	5·1	53	96	355
	After	200	25	42	4·8	51	94	390
F.H.	Before	200	11	23	4·7	112	42	185
	After	200	32	45	3·3	88	38	250
H.B.	Before	205	4	9	4·1	61	67	215
	After	200	9	15	3·3	55	60	215
J.W.	Before	230	8	28	5·4	70	77	300
	After	225	14	27	4·4	63	70	320
C.P.	Before	220	−2	3	3·5	62	57	250
	After	210	−1	5	3·5	57	58	290
Mean	Before	219	7	19	4·7	71	71	285
	After	209	15	26	4·0	62	68	315

* By indicator dilution.

in each subject, giving from 6 to 26 ratios on each occasion. The average of these values was used to calculate the left ventricular end-diastolic volume. The thermo-dilution ratio (r) is a measure of the degree of emptying of the ventricle, and the end-diastolic volume is obtained by dividing the stroke volume by the fraction $1 - r$.

$$r = \frac{ESV}{EDV} = \frac{EDV - SV}{EDV} = 1 - \frac{SV}{EDV}$$

$$\therefore \; 1 - r = \frac{SV}{EDV}$$

$$\therefore \; EDV = \frac{SV}{1 - r}$$

where ESV = end-systolic volume, EDV = end-diastolic volume, and SV = stroke volume.

Four indices of ventricular work were calculated on the assumption that the left ventricle was a spherical chamber with a constant rate of emptying. *Pressure-time per minute*, that is the tension-time index of Sarnoff et al. (1958), was measured as the product of mean ventricular systolic pressure (mm. Hg), the duration of ventricular systole (sec.), and the heart rate (per min.). *Contractile element work* was calculated from the index proposed by Britman and Levine (1964) as the product of mean ventricular systolic pressure (mm. Hg), heart rate (per min.), and a volume factor (ml.). The volume factor consists of the stroke volume plus 10/96 of the mean volume during systole. From the Laplace relation for a sphere, the force per unit of circumference (f) is half the product of the pressure and the radius ($f = \frac{1}{2}Pr$). The total force at the circumference (F) is given by $F = \frac{1}{2}Pr \times 2\pi r = P\pi r^2$, that is, the product of the pressure and the cross-sectional area (πr^2). *Mean systolic force* was therefore calculated as the product of the mean ventricular systolic pressure (mm. Hg) and the mean cross-sectional area (cm.²).

Force-time per minute was calculated as the product of mean systolic force (mm. Hg × cm.²), the duration of ventricular systole (sec.), and the heart rate (per min.).

We have also calculated the mean ventricular emptying rate (ml./sec.) from the stroke volume and ejection time, and the mean circumferential shortening rate (cm./sec.) from the ejection time and the difference between end-diastolic and end-systolic circumference assuming a spherical ventricle.

RESULTS

Cardiac catheterization confirmed the clinical diagnosis of severe aortic stenosis, with peak left ventricular systolic pressures of 200 mm. Hg or more, in all six patients (Table II). The cardiac output measured by the Fick principle early in each study was not seriously reduced in any patient, and the aortic valve area calculated from the hydraulic formula (Gorlin and Gorlin, 1951) was from 0·5 to 0·7 cm.² (Table I).

The administration of 5 mg. propranolol produced little change in peak left ventricular systolic pressure. The cardiac output measured by the indicator dilution method fell in the five subjects with raised left ventricular diastolic pressures, but was unchanged in C.P. who had a normal left ventricular diastolic pressure. The average fall from 4·7 to 4·0 l./min., a reduction of 15 per cent, was statistically significant ((t = 3·08; p < 0·05). There was a consistent fall in heart rate of similar degree, from an average 71 to 62 beats a minute, which was similarly significant (t = 2·58; p < 0·05). One patient (F.H.) had a moderate tachycardia throughout
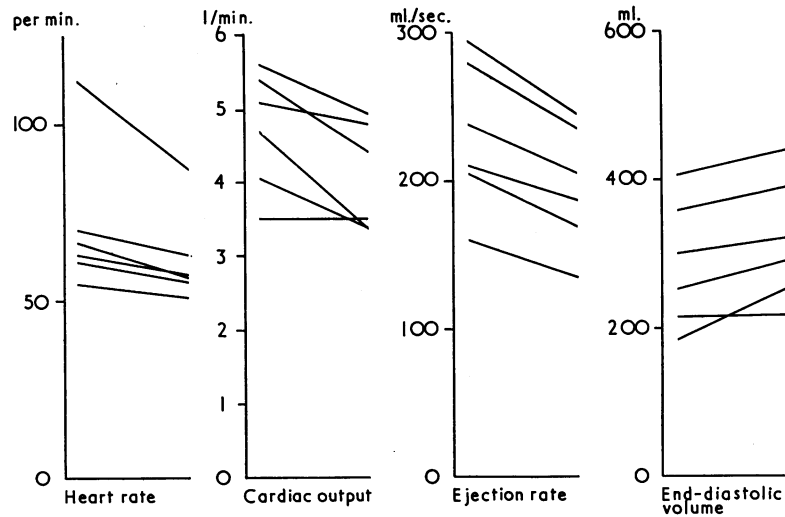
FIG. 2.—Changes in cardiac performance produced by propranolol.
There was a significant fall in heart rate, cardiac output, and mean ejection rate. Left ventricular end-diastolic volume tended to increase.

the study. There was little change in stroke volume (Fig. 2 and Table II).

The left ventricular end-diastolic pressure rose considerably after propranolol in 4 patients. The patient with a normal diastolic pressure in the left ventricle (C.P.) showed little change after the drug (Fig. 3 and Table II). The increase in end-diastolic pressure in these patients was entirely due to a rise in the z point, that is the diastolic pressure immediately before the a-wave (Fig. 4). The in-

crement in pressure due to atrial contraction was unchanged or reduced (J.W.).

The duration of ventricular systole was prolonged by propranolol in 4 and unchanged in 2 patients; the average increase was from 0·45 to 0·48 sec. Because of the bradycardia produced by the drug, the total time occupied by systole was not consistently altered, averaging 36 per cent before and 35 per cent after the drug. There was a tendency for mean ventricular systolic pressure to fall after propranolol,
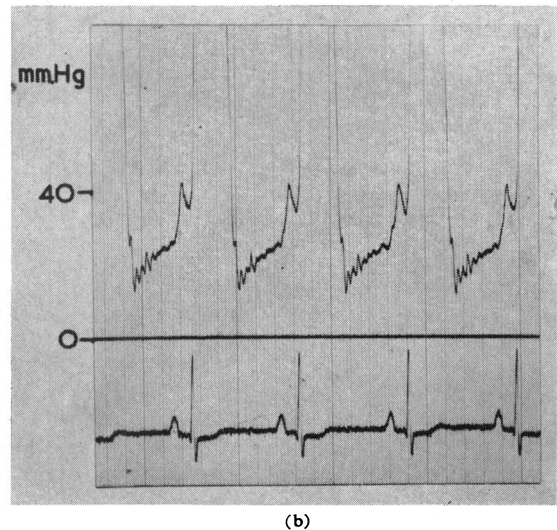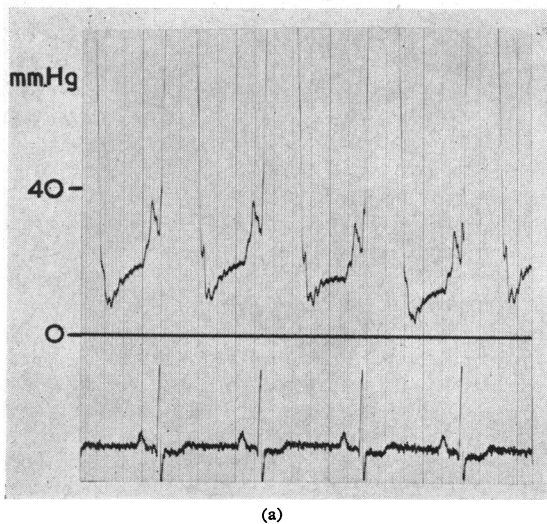

FIG. 3.—An example of the effect of propranolol on left ventricular diastolic pressure, (a) before, and (b) after.

the average changing from 147 to 142 mm. Hg. The pressure-time per minute was consistently reduced, the average falling from 4550 to 4200 mm. Hg sec./min., an 8 per cent decrease ($t=3\cdot15$; $p<0\cdot05$) (Fig. 5 and Table V). Ejection time was prolonged by propranolol in all cases, average values rising from $0\cdot30$ sec. before to $0\cdot34$ sec. after the drug, and the mean ejection rate fell in all cases, from an average of 232 to 195 ml./sec., a 16 per cent decrease; this change was highly significant statistically ($t=7\cdot9$; $p<0\cdot001$) (Fig. 2 and Table V).

A clear stepwise rise in temperature was evident in all the thermodilution curves. From 6 to 26 measurements of the ratio were made on each occasion (i.e. before and after propranolol), in from 2 to 8 curves (Table III). There was no systematic trend for the thermodilution ratio to change during the course of the curve (Table IV). Variance analysis, based on seven occasions on which three or more curves with at least three satisfactory ratios were recorded, showed that the variation in thermodilution rates from curve to curve was not significantly greater than the variation within each curve, using Snedecor's F test.

The number of thermodilution measurements before and after propranolol in each subject is shown in Table III together with the mean values for the thermodilution ratio (r) and the standard deviations. The ratio was consistently increased after proprano-
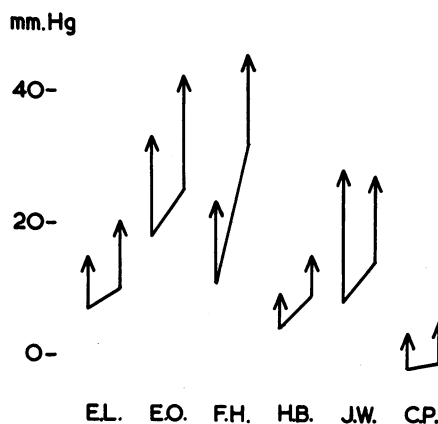

FIG. 4.—Effect of propranolol on the a-wave in the left ventricle in 6 patients with aortic stenosis. The arrows represent the rise in left ventricular diastolic pressure due to left atrial contraction. For each subject the values before propranolol are shown on the left and after propranolol on the right.

lol, and in four subjects Student's t test showed that the increase was statistically significant. Analysis of the pooled data from all six subjects, expressed in terms of the deviation from the mean in each case (Fig. 6), shows a highly significant increase after propranolol by Student's t test.
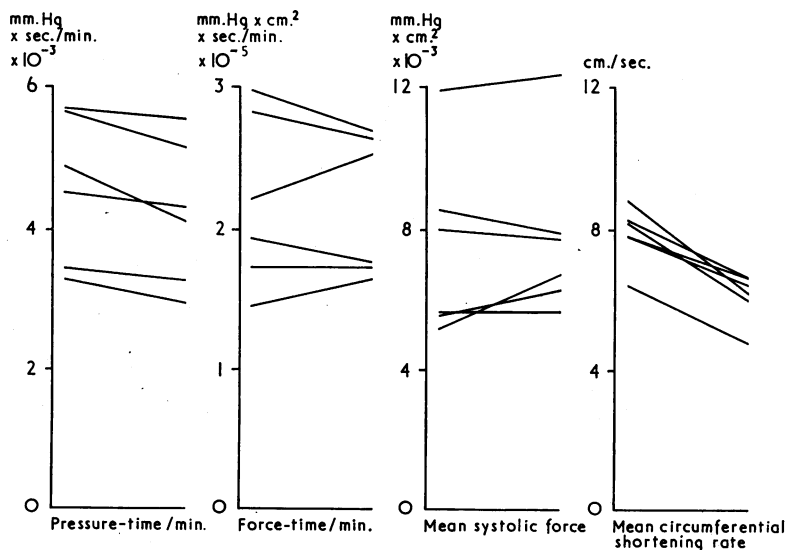

FIG. 5.—Changes in left ventricular work produced by propranolol. There was a reduction in pressure-time per minute, but mean systolic force and force-time per minute show no consistent change. There was a considerable reduction in mean circumferential shortening rate.

TABLE III
THERMODILUTION MEASUREMENTS
BEFORE AND AFTER PROPRANOLOL

Patient		No. of curves obtained	No. of ratios measured	Mean ratio	Standard deviation	Student's t test	Probability (2P)
E.L.	Before	2	8	0·784	0·046	0·4	> 0·6
	After	5	14	0·791	0·035		
E.O.	Before	6	12	0·726	0·022	2·4	< 0·025
	After	6	19	0·764	0·049		
F.H.	Before	5	12	0·770	0·028	7·0	< 0·001
	After	3	12	0·854	0·029		
H.B.	Before	6	20	0·693	0·026	3·4	< 0·005
	After	7	26	0·720	0·024		
J.W.	Before	8	23	0·742	0·025	4·9	< 0·001
	After	7	19	0·781	0·024		
C.P.	Before	5	11	0·772	0·033	1·8	> 0·05
	After	4	6	0·802	0·029		
Total	Before	32	85	0·748	0·029	8·0	< 0·001
	After	32	96	0·785	0·033		

TABLE IV
AVERAGE THERMODILUTION RATIOS FROM CONSECUTIVE BEATS

No. of ratios measured	No. of curves	3/4	4/5	5/6	6/7
3	39	0·763	0·670	0·767	—
4	17	0·764	0·752	0·766	0·751

The mean thermodilution ratio corrected to two significant figures was used in the subsequent calculations. Consistently large values were found in all six patients irrespective of the presence of aortic incompetence. The average change after propranolol, from 0·75 to 0·79, is small in numerical terms, but has a considerable effect on the estimate of end-diastolic volume which is calculated from $1 - r$. The end-diastolic volume was increased in five subjects, and in the other patient, H.B., there was no change. The average increase was from 285 to 315 ml., a rise of 11 per cent (Fig. 2).

There was no consistent change in mean systolic force, the average increasing by 4 per cent. The contractile element work index was consistently and

TABLE V
VENTRICULAR FORCE AND WORK
BEFORE AND AFTER PROPRANOLOL

Patient		Rate (per min.)	Systolic time (sec.)	Total duration of systole (%)	Mean systolic pressure (mm.Hg)	Mean ventricular systolic volume (ml.)	Pressure-time per min. (mm.Hg sec. per min.)	Mean systolic force ($\pi r^2.P \times 10^{-2}$)	Contractile element work index ($\times 10^{-4}$)	Force-time per min. (P.t/min. $\times \pi r^2 \times 10^{-3}$)	Ejection time (sec.)	Mean ejection rate (ml./sec)	Mean circumferential shortening rate (cm./sec.)
E.L.	Before	66	0·46	32	160	360	4850	99	130	300	0·29	295	7·8
	After	56	0·46	34	160	390	4120	104	116	270	0·36	245	6·3
E.O.	Before	53	0·46	30	135	335	3290	80	94	195	0·34	280	8·7
	After	51	0·46	34	125	365	2930	77	84	180	0·40	235	6·1
F.H.	Before	112	0·36	49	140	115	5640	51	93	220	0·26	160	6·3
	After	88	0·43	41	145	230	5480	67	79	250	0·28	135	4·7
H.B.	Before	61	0·51	37	145	180	4510	56	76	175	0·33	205	8·2
	After	55	0·56	36	140	190	4310	56	62	175	0·36	165	6·4
J.W.	Before	70	0·47	37	170	260	5590	85	124	280	0·32	240	7·8
	After	63	0·52	36	155	270	5080	79	96	260	0·34	205	6·5
C.P.	Before	62	0·43	28	130	205	3470	55	63	145	0·27	210	8·2
	After	57	0·46	29	125	260	3280	62	61	165	0·31	185	5·9
Mean	Before	71	0·45	36	147	250	4550	71	97	219	0·30	232	7·8
	After	62	0·48	35	142	285	4200	74	83	217	0·34	195	6·0

significantly reduced (t = 3·96; p < 0·05), falling on the average by 14 per cent. Force–time per minute showed no consistent change (average 1% fall). The mean circumferential shortening rate was considerably reduced in all subjects, falling on average from 7·8 to 6·0 cm./sec., a reduction of 23 per cent; this change was highly significant statistically (t = 8·1; p < 0·001) (Fig. 5 and Table V).

FIG. 6.—Thermodilution ratio before and after propranolol. The data from all six subjects with aortic stenosis expressed in terms of deviation from the individual mean are shown as a scatter diagram around the over-all average value. There is an approximately normal distribution of the results both before and after propranolol, and the difference is highly significant (t = 8·0, p < 0·001).

DISCUSSION

Thermodilution Measurements. Possible sources of error in the measurement of left ventricular volume by the thermodilution method are considered by Rolett, Sherman, and Gorlin (1964). If the response of the sensor to change in temperature is unduly slow the steps of the washout curve may be slurred, but the response of the thermocouple used in the present study was sufficiently fast to give clear steps with each heart beat (Fig. 1). Incomplete mixing of indicator is a source of error in all indicator dilution methods. Injection through a catheter with multiple holes at the tip increases the mixing of the indicator within the ventricle, but it is difficult to exclude a peripheral position of the catheter tip which may make the distribution of indicator in the ventricle uneven. As the first three beats after injection of the indicator are disregarded, free mixing of the indicator is thought to occur before any

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measurements are made. The absence of any systematic change in the washout ratio measured at subsequent beats in the present study (Fig. 1) confirms that no further mixing is in fact occurring.

It has been suggested that only part of the left ventricular cavity takes part in systolic ejection and that part of the residual blood remains unmixed with incoming blood from the left atrium. Incomplete mixing may lead to preferential ejection of warm blood from the atrium, producing, with the convention used here, an upward slope to the steps of the ventricular washout curve as colder blood is ejected later in systole. Any indicator remaining in this inert pool will not appear in the aorta and will give rise to unduly small washout ratios and left ventricular volumes. However, if indicator from the inert pool is gradually added to the ejectate, the washout ratios and left ventricular volumes will be increased. The net effect of this hypothetical inert residual blood in the left ventricle is therefore difficult to predict. Mitral incompetence will, of course, lead to an overestimate of left ventricular volume and was excluded on clinical, hæmodynamic, and angiocardiographic grounds in the present study.

The position of the transducer in the ascending aorta is not critical. Under normal circumstances the flat velocity profile of blood ejected into the aorta ensures that the ascending portion becomes filled by blood from the left ventricle at each systole. In aortic stenosis mixing due to the jet from the aortic orifice will distort the even filling of the ascending aorta, but the turbulence rapidly produces a flat velocity profile.

In aortic incompetence the increased turbulence leads to the rapid formation of a flat velocity profile, and blood from the previous beat will not return to the site of the transducer in the ascending aorta during diastole unless the regurgitant flow is very great. The present study was restricted to patients with aortic stenosis who had only slight or moderate incompetence, and under these circumstances the left ventricular end-diastolic volume can be calculated satisfactorily from the effective stroke volume, but the end-systolic volume will be overestimated by the amount of the regurgitant flow. No significant change in arterial pressure or effective stroke volume was seen after propranolol, so the alterations in ventricular volume found here cannot be attributed to variations in the degree of aortic incompetence.

A problem with thermodilution techniques which is not found with other indicators is exchange of heat with the surrounding structures, i.e. the left ventricular wall. As the indicator is not confined to the circulation the volume measured must in-

clude a portion of the left ventricular muscle. Much of the indicator is washed out of the ventricular wall in the same way as from the cavity, though with less satisfactory mixing. This effect is probably responsible for the apparently unmixed left ventricular compartment discussed previously, and may lead to unduly large values for the washout ratio. Some cold is lost to the coronary circulation, but the magnitude of this error can be calculated from measurement of the amount of cold blood entering the aorta. Rolett et al. (1964) estimate that the error in the measurement of the ratio from these sources is less than 5 per cent.

The errors of measurement are necessarily greater at larger washout ratios (r) as the volume measurements are derived by dividing stroke volume by $1 - r$ which of course falls rapidly as r approaches unity. In spite of the inevitable errors in this method it seems clear that the thermodilution technique gives an indication of left ventricular end-systolic and end-diastolic volumes, and might be expected to show the direction and magnitude of any changes. The results of left ventricular volume measurements in aortic stenosis by this technique and by angiocardiography will be reported elsewhere (Fleming and Hamer, in preparation). The large values for the thermodilution ratio, indicating that only a small fraction of the left ventricular blood is ejected during systole, are similar to those reported with the thermodilution method in aortic stenosis by other workers (Gorlin et al., 1964).

Ventricular Work. The external ventricular work measured as the product of pressure and volume of blood ejected from the chamber during systole, plus velocity and acceleration factors, is an inadequate index of the work performed by the ventricular myocardium. External work in fact forms only a small proportion of the myocardial work, indicating a low efficiency for the heart as a pump, and the additional work appears as heat. In the assessment of myocardial function an estimate of internal work is necessary. Myocardial oxygen consumption is a useful indication of internal work when metabolism is aerobic, and can be used to determine the accuracy of measurements of ventricular work derived from the mechanical events in the heart.

An estimate of the work done by the myocardium can be obtained from the magnitude and duration of the tension developed in the wall of the ventricle during systole. The pressure–time per minute was used by Sarnoff et al. (1958) in an attempt to assess the total tension for the whole of systole from the pressure in the ventricle and the duration of contraction. However, the wall tension depends not only on the intracavity pressure but also on the

volume of the chamber, and this factor must be taken into consideration in estimating alterations in myocardial work when the ventricle changes in size.

Calculations based on the assumption that the ventricle is a sphere do not give rise to serious error (Gorlin et al., 1964), and from the Laplace relation the total tension in the walls of the ventricle may be expressed as $T = \pi r^2 P$ (Burton, 1957), where r is the radius of the ventricle and P the intraventricular pressure. In the present study these calculations are applied to the average situation during systole. An index of myocardial work based on the tension developed in the ventricular wall must include the mean systolic pressure and the duration of systole, as in the pressure-time per minute, and a factor related to the volume of the chamber during systole. A further complication is the presence of non-contractile elements in the heart muscle; Britman and Levine (1964) have been able to take this factor into account and have produced the empirical formula for contractile element work which we have used; however, this formula does not consider the effect of variations in the duration of systole.

The use of force-time per minute as an index of myocardial work has the advantage that both the ventricular volume used in the calculation of mean systolic force and the duration of systole are taken into consideration. This index does not take into account the effect of non-contractile elements, but this is probably not a serious deficiency once the fibres have been stretched at the beginning of systole (Sonnenblick, 1965). Pressure-time per minute, contractile element work index, and force-time per minute have been shown to be closely related to myocardial oxygen consumption over a wide range of conditions (Britman and Levine, 1964), and are therefore satisfactory estimates of total left ventricular work under appropriate circumstances. Force-time per minute seems the logical estimate of ventricular myocardial work for the present study as both ventricular volume and the duration of systole are altered by sympathetic blockade.

A slight fall in mean left ventricular systolic pressure was found after propranolol in our patients. Systole was prolonged but the rate fell so the total time occupied by systole was little affected. The average pressure-time per minute therefore fell by 8 per cent (Fig. 5). On the other hand ventricular end-diastolic volume tended to increase and there was little change in stroke volume, so that, assuming even emptying throughout systole, the average mean systolic volume was increased by 14 per cent after propranolol. Both mean systolic force, which expresses the tension in the left ventricular wall and combines the effect of lower systolic pressure and larger systolic volume, and force-time per minute,

which includes the effect of changes in the duration of systole and seems the best index of the work done by the ventricular muscle under the present circumstances, show no consistent change (Fig. 5). The contractile element work index of Britman and Levine (1964) shows a 14 per cent fall after propranolol, but this is due to the slower heart rate and the failure of this index to take into account changes in the duration of systole. We conclude that these measurements of ventricular wall tension show no significant change in myocardial work after propranolol.

Similar effects have been reported after propranolol in dogs by Murray *et al.* (1966). Surprisingly, they found no change in heart rate or cardiac output, but the left ventricular end-diastolic pressure increased, as did the thermodilution ratio, and there was a tendency to a larger end-diastolic volume. On the other hand Shanks (1966) found between 10 and 20 per cent reduction in ventricular contractile force measured directly with a strain gauge arch in the dog after propranolol, though there was a reduction in heart rate, blood pressure, and aortic flow.

A similar study of a mixed group of normal subjects and patients with ischæmic heart disease (Wolfson *et al.*, 1966) has shown a tendency to a fall in ventricular volume and in force-time per minute after propranolol, which is consistent with the suggestion (Hamer and Sowton, 1965) that a reduction in myocardial work is responsible for the beneficial effect of propranolol in angina. Our findings in patients with severe left ventricular hypertrophy due to aortic stenosis do not support this hypothesis.

Velocity of Contraction. The fall in cardiac output after propranolol in the present study is similar to that found in patients with angina pectoris (Hamer and Sowton, 1965) and in normal subjects (Epstein *et al.*, 1965). The reduction in output is chiefly related to the slower heart rate after the drug; there is little change in stroke volume and systole tends to be prolonged, suggesting that the velocity of contraction of the ventricular muscle is reduced. This is confirmed by direct measurement which shows a fall in mean ejection rate by an average of 16 per cent (Fig. 2) and in mean circumferential shortening rate by 23 per cent (Fig. 5) after beta-adrenergic blockade. Murray *et al.* (1966) found a similar reduction in mean circumferential shortening rate after propranolol in the dog, and the reverse effect was reported by Gorlin *et al.* (1964) after beta-sympathetic stimulation with isoprenaline; this drug produced little change in the mean systolic force in the left ventricular wall in normal subjects,

but there was some increase in force in patients with aortic stenosis. Wolfson *et al.* (1966), on the other hand, report a tendency to an increased mean circumferential shortening rate after propranolol in their normal subjects and patients with ischæmic heart disease, in association with a tendency to a reduction in systolic force.

The reduced velocity of contraction of the ventricular muscle after propranolol in our patients with aortic stenosis is probably responsible for the slower ejection rate. The larger left ventricular volume helps to compensate for the reduced velocity of contraction, as less shortening of the wall is needed to produce the same stroke volume in a larger ventricle (Gorlin, 1962). Nevertheless the interference with myocardial contractility seems to prevent adequate compensation for the bradycardia produced by the drug so that the cardiac output falls. The handicap of a slow ejection rate will be particularly noticeable during tachycardia, for instance, on exercise.

Ventricular performance may also be analysed on the basis of the relation between the force and velocity of contraction and the length of the muscle fibres (Levine and Britman, 1964; Downing and Sonnenblick, 1964; Fry, Griggs, and Greenfield, 1964). The force of contraction increases with the length of the muscle fibre, and at any particular fibre length the velocity of contraction falls as the force of contraction increases. This concept appears to be applicable throughout systole, and to be relatively unaffected by non-contractile elements (Sonnenblick, 1965). The increased force of contraction produced by the Starling mechanism when the initial fibre length is increased is an example of the relation between force and fibre length. An increase in wall tension would be expected to reduce the velocity of shortening, and this may play a part in reducing the efficiency of the dilated ventricle in heart failure in which wall tension is necessarily increased if the systolic pressure is maintained (Gorlin, 1962). The velocity of contraction varies independently of the force-length relation in response to inotropic effects such as adrenergic stimulation (Sonnenblick *et al.*, 1964).

These concepts may be applied to the mean values of systolic force and circumferential shortening rate obtained in the present study. The increase in fibre length associated with the greater ventricular volume after propranolol would be expected to increase systolic force, but this effect is counteracted by the slight fall in ventricular systolic pressure so that no consistent change in fact occurs. The effect of propranolol is mainly evident as a reduction in the velocity of contraction as expressed by the fall in circumferential shortening rate. The lower

heart rate produced by propranolol would be expected to lead to a slower contraction, as Sonnenblick, Morrow, and Williams (1966) have shown a close relation between heart rate and the rate of development of force in the ventricular wall. However, the considerable fall in circumferential shortening rate found in the present study seems too great to be accounted for by the bradycardia alone.

Recent work (Sonnenblick et al., 1965) has suggested that the velocity of contraction is a major determinant of myocardial oxygen consumption. As the velocity of contraction is not taken into consideration in calculating indices of ventricular work such as force-time per minute discussed previously, these indices probably give an incomplete estimate of myocardial oxygen consumption. The reduction in circumferential shortening rate demonstrated after propranolol in the present study may therefore be associated with a reduction in myocardial oxygen consumption even though the force-time per minute is unchanged. A similar effect is envisaged by Britman and Levine (1964) who found that myocardial oxygen consumption was disproportionate to contractile element work after isoprenaline. The improvement in exercise tolerance in patients with angina after propranolol may be due to a reduction in oxygen consumption resulting from a slower velocity of contraction in the myocardium.

Ventricular Diastolic Tone. The relatively small increase (11%) in end-diastolic volume in the left ventricle after propranolol is associated with a considerable increase in left ventricular end-diastolic pressure in the five patients in this study with high pressures before the drug was given. These pressure measurements are referred to an arbitrary baseline at the sternal angle. Accurate assessment of the pressure distending the ventricle requires measurement of the intrapericardial pressure, which is probably between −5 and −10 mm. Hg below the reference level. The distending force on the myocardium is therefore greater than expected from the pressure measurements referred to the sternal angle. The pressure at the peak of the a-wave rose on the average from 19 to 26 mm. Hg above the sternal angle after propranolol in the present study. If an intrapericardial pressure of −10 mm. Hg is assumed, the increase in transmural pressure is from 29 to 36 mm. Hg, a rise of 24 per cent. This increase in pressure in association with a smaller (11%) increase in volume is not necessarily to be considered as evidence that there has been an increase in the stiffness of the left ventricular wall in diastole. Mitchell, Linden, and Sarnoff (1960) have shown that changes in sympathetic tone do not affect left ventricular diastolic compliance except

perhaps at fast heart rates, and the present findings are best explained by the assumption that the ventricle is operating on a relatively steep part of the diastolic pressure-volume curve after propranolol in these patients.

The rise in left ventricular pressure during the a-wave is due entirely to an increase in pressure before the a-wave (z point) (Fig. 4), and the increment in pressure produced by atrial systole is unchanged by propranolol. These findings are consistent with our observations using the apexcardiogram (Fleming and Hamer, 1967) in other types of left ventricular disease, which suggested that propranolol reduced atrial contractility. The increased atrial distension before atrial systole, which might be expected to augment atrial contractility by the Starling mechanism, is probably counteracted by the loss of the effect of sympathetic stimulation on the atrium. An increase in atrial contraction to distend the ventricle further and produce a greater ventricular contraction by the Starling mechanism seems, therefore, to be hampered by propranolol, so that a possible mechanism which might augment ventricular contractility cannot operate.

The increase in left ventricular end-diastolic pressure seen after propranolol probably represents a compensatory response to the reduction in ventricular contractility. If the muscle fibres are stretched, contractility may be increased by the Starling mechanism. However, there is evidence (Linzbach, 1960) that the muscle fibres slide over one another as the ventricle distends, so that the increase in the resting tension in the individual fibres is difficult to assess. A greater systolic force must necessarily be developed in the wall of a dilated ventricle if the systolic pressure is to be maintained. In the present study there was no consistent change in mean systolic force after propranolol as mean systolic pressure was reduced. A greater diastolic volume offers a mechanical advantage in that less shortening of the ventricular wall is needed for a given stroke volume (Gorlin, 1962), and the increase in diastolic volume after propranolol may help the ventricle to produce an unchanged stroke volume in spite of a reduced circumferential shortening rate. This mechanism seems to outweigh the need for an increase in total wall tension. Further operation of the Starling mechanism to allow a larger stroke volume and a normal cardiac output in spite of the bradycardia is probably prevented by the steepness of the ventricular diastolic pressure-volume curve. In the presence of reduced left atrial contractility a prohibitive rise in left ventricular diastolic pressure would be required to maintain the cardiac output by this mechanism in our patients.

Importance of Sympathetic Activity in Heart Disease. The conflicting evidence of increased urinary catecholamine excretion and decreased myocardial catecholamine concentration in heart failure leaves doubt as to the importance of sympathetic activity in the myocardium in this situation. Braunwald and Chidsey (1965) report that sympathetic stimulation in experimental heart failure in animals produces a reduced release of noradrenaline, and suggest that the depletion of myocardial catecholamines may be an indication that the beneficial effects of adrenergic activity are lost in heart failure. Our findings do not support this view. The patients studied here have severe left ventricular disease with high left ventricular diastolic pressures, but show serious further deterioration when sympathetic activity is blocked by propranolol. It seems clear that in these patients sympathetic activity plays a major part in maintaining myocardial contractility even at rest.

It is clearly important to avoid beta-adrenergic blockade in patients with severe myocardial disease, as this study shows an increase in end-diastolic pressure and volume, which indicates that left ventricular failure may be precipitated by propranolol. On the other hand the loss of adrenergic activity is well tolerated by patients with relatively normal left ventricular function (e.g. C.P.), and would not be expected to produce left ventricular failure in most patients with angina. The appearance of a rise in ventricular end-diastolic pressure from previously normal values after propranolol may be an indication of incipient failure, but was not observed here. Most of our patients under consideration for aortic valve replacement show seriously raised pressures under control conditions. The response to propranolol is in fact a measure of the adrenergic stimulus to the myocardium, and this study has shown the importance of sympathetic activity in maintaining myocardial contractility in severe heart disease.

SUMMARY

The changes in left ventricular work produced by propranolol have been measured in six patients with severe aortic stenosis. Left ventricular volume was obtained by thermodilution using a thermocouple with a fast response. Possible errors in the thermodilution method are discussed.

A significant reduction in heart rate and cardiac output was found after propranolol, and the mean ventricular ejection rate was reduced. There was a significant increase in the thermodilution ratio, indicating an increase in left ventricular end-diastolic volume, and left ventricular end-diastolic pressure tended to rise after propranolol.

Force-time per minute was selected as the best index of left ventricular work as it is sensitive to changes in ventricular volume and in the duration of systole. By this criterion there was no change in left ventricular work after propranolol. However, the mean circumferential shortening rate was consistently reduced, and this change probably leads to a lower myocardial oxygen consumption.

It is concluded that the primary effect of propranolol is to reduce the velocity of myocardial contraction. The fall in cardiac output and the increase in left ventricular end-diastolic volume and pressure after propranolol in these patients indicate that sympathetic nervous activity plays an important part in the response of the left ventricle to aortic stenosis.

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