Action of Propranolol on Left Ventricular Contraction in Aortic Stenosis When a Fall in Heart Rate is Prevented by Atropine

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A previous study of the changes in left ventricular pressure and volume produced by propranolol in patients with severe aortic stenosis (Hamer and Fleming, 1967) indicated a reduction in the velocity of myocardial contraction after this drug. However, a major action of propranolol is to reduce the heart rate, and as bradycardia may be associated with a reduction in the velocity of contraction it was not clear whether we were producing a true effect on contractility other than that which might be expected from the slower rate. In the present study the bradycardia that follows the administration of propranolol has been prevented by giving a large dose of atropine. Any changes in the force or velocity of contraction of the left ventricular muscle under these circumstances can be attributed to a direct action of propranolol on the myocardium.

METHODS

Left ventricular pressure and volume were measured before the administration of any drug, and the measurements were repeated after the administration of propranolol and atropine. The studies were carried out as part of the routine catheterization in 6 patients being assessed for aortic valve replacement. In all cases there was severe obstruction at the aortic valve, though a minor degree of aortic incompetence was present in one subject.

Cardiac catheterization was performed from the right saphenous vein without premedication. Pressures were measured with a P23Db Statham strain gauge and a N.E.P. photographic recorder at a paper speed of 80 mm./sec., using the sternal angle as the zero reference level. Cardiac output was measured by the indicator dilution technique using a Gilford cuvette and indocyanine green. The indicator dilution curves were calibrated by the dynamic method (Shinebourne, Fleming, and Hamer, 1967). After catheterization of the right heart, a Brockenhough catheter was inserted and the left ventricle was entered by transseptal puncture. The

dye was injected into the left ventricle and a No. 6 Teflon Gensini catheter was placed in the right femoral artery by the percutaneous method to record the indicator dilution curves. The Gensini catheter was advanced to the ascending aorta about 1 cm. above the aortic valve and the pressure gradient at the aortic valve and the left ventricular diastolic pressure recorded. A chromel-constantin thermocouple wire (Watson and Fleming, 1968) was inserted into the aortic catheter until it just protruded from the tip. Multiple injections of between 5 and 10 ml. of ice-cold saline were given into the left ventricle, and the thermodilution curves from the aortic thermocouple were recorded photographically. 5 mg. propranolol and 2.4 mg. atropine were injected into the left ventricle in 1 minute. After 10 minutes the thermodilution curves were repeated. The thermocouple was then withdrawn and further pressure measurements and indicator dilution curves obtained. The thermodilution curves and the measurements of cardiac output by indicator dilution were performed within a 10-minute period without evident change in the state of the patient.

The ratio between the steps of the thermodilution curve was measured, beginning from the fourth beat after the appearance of the indicator and continuing until accurate measurement became difficult. If an ectopic beat occurred no measurements were made until there had been two subsequent normal beats. Up to 5 measurements were made on each curve, and from 3 to 6 curves were obtained in each part of the study in each subject, so that the value for the thermodilution ratio (r) used to calculate the left ventricular end-diastolic volume was the mean of from 7 to 20 observations. The ratio is a measure of the degree of emptying of the ventricle, and the end-diastolic volume is obtained by dividing the stroke volume, calculated from the cardiac output and heart rate, by the fraction $1-r$.

Left ventricular systolic time was measured from amplified records of left ventricular diastolic pressure on a scale of 10 mm. Hg/cm. and a paper speed of 75 cm./sec. Left ventricular ejection time was measured from simultaneous records of aortic and left ventricular pressure on a scale of 50 mm. Hg/cm. and the same paper

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speed. 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.). Other indices of ventricular work were calculated on the assumption that the left ventricle was a spherical chamber with a constant rate of emptying. 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 $F = \frac{1}{2}Pr \times 2\pi r = \pi P \times r^2$, that is the product of the pressure and the cross-sectional area (πr^2). Mean systolic force in the ventricular wall was therefore determined as the product of the mean ventricular systolic pressure (mm. Hg) and the mean cross-sectional area (cm.²). Force-time per minute was estimated as the product of mean systolic force (mm. Hg $\times$ cm.²), the duration of ventricular systole (sec.), and the heart rate (per min.). We also calculated the mean ventricular ejection rate (ml./sec.) from the stroke volume and ejection time. The mean circumferential

shortening rate was obtained from the ejection time and the difference between end-diastolic and end-systolic circumference assuming a spherical ventricle, and was expressed in cm./sec. and in terms of change in the mean circumference per sec.

TABLE I
CLINICAL ASSESSMENT AND CATHETERIZATION FINDINGS

Case No.	Age (yr.)	Sex	Degree of aortic incompetence (0-4)	Body surface area (m. ²)	Cardiac output (l./min.)	Aortic valve area (cm. ²)
1	56	M	0	1.96	3.5	0.4
2	40	M	1	1.84	3.0	0.6
3	58	F	0	1.83	6.6	0.6
4	49	F	0	1.58	3.4	0.4
5	55	M	0	1.75	4.7	0.4
6	49	M	0	1.94	5.4	0.7

TABLE II
HAEMODYNAMIC MEASUREMENTS BEFORE AND AFTER PROPRANOLOL AND ATROPINE

Case No.		LV systolic pressure (mm. Hg)	LV diastolic pressure (mm. Hg) z a	PR interval (sec.)	Cardiac output (l./min.)	Heart rate/min.	Stroke volume (ml.)	LV end-diastolic volume (ml.)
1	Before	185	2 5	0.20	3.5	79	45	170
	After	190	2 7	0.21	2.6	86	30	130
2	Before	170	7 18	0.23	3.0	71	42	205
	After	155	0 10	0.23	3.0	81	37	190
3	Before	240	6 12	0.16	6.6	81	82	195
	After	230	6 14	0.18	5.7	83	69	175
4	Before	195	5 12	0.13	3.4	81	42	125
	After	205	5 10	0.14	3.4	94	36	130
5	Before	270	15 22	0.16	4.7	98	48	155
	After	240	10 25	0.18	3.7	89	42	145
6	Before	180	8 16	0.14	5.4	72	75	300
	After	185	5 10	0.15	4.5	81	54	235
Mean	Before	195	7 14	0.17	4.4	80	56	190
	After	200	5 13	0.18	3.8	85	45	180

FIG. 1.—The change in heart rate, cardiac output, mean ejection rate, and end-diastolic volume of the left ventricle (measured by the thermodilution method) in 6 patients with aortic stenosis after propranolol 5 mg. and atropine 2.4 mg. The bradycardia usually produced by propranolol is prevented by atropine, but cardiac output and ejection rate are reduced.

RESULTS

The cardiac catheterization findings confirmed the clinical diagnosis of severe aortic stenosis in each patient (Table I). The cardiac output was often below normal, the left ventricular systolic pressure was considerably raised, and some patients had a high left ventricular end-diastolic pressure. The similarity of the calculated aortic valve area before and after the drugs confirmed the accuracy of the pressure and flow measurements.

The combination of 5 mg. propranolol and 2.4 mg. atropine led to a slight increase in heart rate in 5 of the 6 patients, the average rate rising from 80 to 85/min. (Table II and Fig. 1). Cardiac output, measured by the indicator dilution technique, fell in 4 patients and was unchanged in the other 2, giving a significant fall from 4.4 to 3.8 l./min. ($p < 0.05$) on average. Stroke volume was consistently reduced, the average falling from 56 to 45 ml. ($p < 0.02$). There was little change in left ventricular systolic or diastolic pressure, and though

the P-R interval was usually increased the change was only 0.01 or 0.02 sec.

The duration of left ventricular systole was little affected by the drugs, and there was no consistent change in ejection time. As might be expected under these circumstances, there was little alteration in pressure-time per minute. The mean systolic ejection rate, however, was consistently reduced, giving an average fall from 195 to 155 ml./sec. ($p > 0.01$).

The thermodilution ratio was consistently increased, from a mean of 0.70 to 0.73 ($p < 0.02$), indicating less complete emptying of the ventricle at each beat. The number and scatter of thermodilution measurements in each patient are shown in Table III. In 3 cases, the difference before and after the drugs was statistically significant. The trend was similar in the other 3 subjects, and the pooled results, expressed in terms of deviation from the mean of each patient, show a highly significant increase after propranolol and atropine. The

TABLE III
THERMODILUTION MEASUREMENTS BEFORE AND AFTER PROPRANOLOL AND ATROPINE

Case No.		No. of curves	No. of ratios	Mean ratio	SD	t	p
1	Before	5	16	0.739	0.027	3.8	< 0.001
	After	4	17	0.769	0.015		
2	Before	6	20	0.784	0.017	5.5	< 0.001
	After	5	18	0.803	0.014		
3	Before	5	8	0.581	0.018	0.9	> 0.3
	After	5	10	0.604	0.025		
4	Before	6	11	0.658	0.029	4.2	< 0.001
	After	4	7	0.720	0.028		
5	Before	5	10	0.690	0.042	1.3	> 0.2
	After	5	10	0.713	0.034		
6	Before	3	9	0.752	0.019	1.7	> 0.05
	After	3	10	0.767	0.017		
Total	Before	30	74	0.701	0.026	6.8	< 0.001
	After	26	72	0.728	0.022		

TABLE IV
VENTRICULAR FORCE AND VELOCITY MEASUREMENTS

Case No.		Systolic time (sec.)	Mean LV systolic pressure (mm. Hg)	Pressure-time per min. (mm. Hg sec./min.)	Mean systolic force (mm. Hg/cm. ²)	Force-time per min. (mm. Hg sec. cm. ² /min. $\times 10^{-3}$)	Ejection time (sec.)	Mean ejection rate (ml./sec.)	Mean circumferential shortening rate	
									(cm./sec.)	(circumferences/sec.)
1	Before	0.430	125	4300	4200	145	0.300	150	7.3	0.35
	After	0.380	125	4200	3300	120	0.310	100	5.6	0.30
2	Before	0.410	135	3700	5300	145	0.280	155	6.5	0.29
	After	0.410	115	3800	4300	140	0.280	130	5.8	0.27
3	Before	0.365	180	5300	6200	184	0.285	290	6.6	0.32
	After	0.390	170	5500	5500	178	0.300	230	5.6	0.28
4	Before	0.395	155	5000	4100	131	0.295	140	8.2	0.45
	After	0.380	160	5700	4500	161	0.275	130	7.2	0.38
5	Before	0.365	175	6300	5500	197	0.290	165	8.3	0.42
	After	0.395	170	5800	5100	175	0.295	140	7.4	0.38
6	Before	0.390	120	3400	5900	166	0.285	265	8.3	0.32
	After	0.400	130	4200	5500	178	0.280	195	7.1	0.28
Mean	Before	0.41	150	4700	5200	161	0.31	195	7.5	0.36
	After	0.41	145	4900	4700	159	0.31	155	6.4	0.32

FIG. 2.—The effect of propranolol 5 mg. and atropine 2.4 mg. on three indices of left ventricular wall force and on the mean circumferential shortening rate. There is little change in the force measurements, but the consistent fall in mean circumferential shortening rate indicates a reduction in the velocity of contraction of the muscle fibres in the left ventricular wall.

thermodilution ratios corrected to 2 significant figures were used in the subsequent calculations. Calculated left ventricular end-diastolic volume, derived from the thermodilution ratio and the stroke volume measurement, showed no consistent change.

Mean systolic force, which depends on pressure and volume, fell from 5200 to 4700 $\text{cm}^2 \text{ mm. Hg}$ on average, but the value increased in one patient and the changes were not significant (Table IV and Fig. 2). Force-time per minute, which takes heart rate and the duration of systole into consideration, showed no consistent change. Measurement of the mean circumferential shortening rate showed a consistent and significant fall, from 7.5 to 6.4 cm./sec. ($p < 0.001 \text{ cm./sec.}$), largely related to the reduction in stroke volume. These findings are similar when the results are expressed in terms of mean ventricular circumference.

DISCUSSION

A clear step-wise increase in temperature was evident in all the thermodilution curves used in the present study. Systematic analysis of thermodilution curves (Hamer and Fleming, 1967) suggests that the technique gives a satisfactory estimate of left ventricular volume under the conditions of the present study. The close agreement between left ventricular diastolic volumes measured by this technique and by angiocardigraphy (Fleming and Hamer, 1968) gives further confidence in the validity of the method. Though there is considerable variation in the thermodilution ratio, the ability to

carry out repeated estimates allows the demonstration of a consistent difference before and after the drugs, which in three cases reaches statistical significance. The pooled data show a very significant increase in the mean value after propranolol and atropine.

The alterations in thermodilution ratio indicate a lesser degree of emptying of the ventricle at each beat, which might be considered, in itself, an index of impaired contractility. As the combination of propranolol and atropine in our patients led to a reduction in cardiac output and stroke volume, little alteration is evident in the calculated end-diastolic volume of the left ventricle, which is derived from the stroke volume and the thermodilution ratio.

Measurement of the left ventricular volume is of importance in the assessment of myocardial performance, as changes in the size of the chamber indicate alterations in myocardial performance which are not evident from measurements of ventricular pressure and stroke volume. When ventricular volume measurements are available it is possible to calculate the force and velocity of contraction of the muscle in the ventricular wall. These measurements give a more complete picture of the behaviour of the heart muscle than other estimates of ventricular performance (Covell *et al.*, 1966). The oxygen consumption of the myocardium is probably related to the force developed in the ventricular wall, the duration of the contraction, and the velocity of contraction of the muscle fibres (Sonnenblick *et al.*, 1965), though the relative importance of each of these factors is not known at present.

The thermodilution technique gives estimates of ventricular volume at the end of systole and at the end of diastole, so we can calculate only the mean force and velocity of contraction in the ventricular wall. We cannot take into consideration the effect of variations during the course of ventricular systole. We have also neglected the energy wasted, particularly in the early part of systole, in stretching the parts of the ventricular wall which are not capable of contraction. However, there is evidence that the effect of these non-contractile elements in the muscle fibres is not of major importance (Sonnenblick, 1965), and the calculations which have been proposed to take this effect into consideration involve only a relatively small correction to the force measurements (Britman and Levine, 1964). Our work is confined to patients with severe aortic stenosis, in which the left ventricle is operating against a fixed orifice resistance, so that any peripheral vascular changes will have little effect.

We have calculated three estimates of the force developed in the left ventricular wall (Table IV and Fig. 2). *Pressure-time per minute* is derived from the mean ventricular systolic pressure and the time occupied by systole; this index does not take ventricular volume changes into consideration. *Mean systolic force* is based on ventricular pressure and volume measurements, but does not involve measurement of the duration of contraction. *Force-time per minute* combines these two measurements and takes into consideration ventricular pressure and volume as well as the time occupied by systole. The mean circumferential shortening rate is used as a measure of the velocity of contraction. No clear-cut choice can be made between these indices as estimates of myocardial oxygen consumption. There is a reciprocal relation between the force and the velocity of contraction of heart muscle, so clearly both aspects must be considered. However, the velocity of contraction is also affected by the duration of systole, i.e. a prolonged systole is necessarily associated with a slow contraction, and the net effect on oxygen consumption is not evident. It is not, therefore, possible to construct an over-all index of the energy used by the ventricle, and the changes in force and velocity of ventricular contraction must be considered separately.

Recent work has shown evidence of reduced ventricular contractility after vagal stimulation in animals (DeGeest *et al.*, 1965; Daggett *et al.*, 1967), but there is little evidence of such an effect in man. However, atrial contractility is under vagal control, and after atropine a greater atrial contraction may have an indirect effect on left ventricular work as a result of an increase in ventricular end-diastolic pressure. Atropine in the dose used here has been

shown to produce almost complete vagal block (Chamberlain, Turner, and Sneddon, 1967), and the absence of any noticeable change in the height of the "a" wave in the left ventricular diastolic pressure in our patients suggests that an increase in atrial contractility from a reduction in vagal tone may counteract the adverse effect from propranolol noted in our previous work (Hamer and Fleming, 1967).

The net effect of atropine and propranolol on heart rate was to produce a slight tachycardia in all except one patient, who had a rapid initial heart rate. As there was little alteration in left ventricular systolic pressure or the duration of systole, pressure-time per minute did not change significantly. The changes in the systolic force in the ventricular wall, which are derived from both pressure and volume measurements, were not significant, though a tendency towards a lower value after the drugs is noticeable. When the effect of the changes in rate and duration of systole are taken into consideration and force-time per minute is calculated, no consistent trend is evident. Force-time per minute seems the most complete estimate of the aspect of myocardial consumption concerned with ventricular wall tension.

The velocity of contraction of the muscle fibres in the ventricular wall showed a consistent fall after atropine and propranolol. The reduction in mean ejection rate cannot, in itself, be taken as a definite indication of a lower velocity of contraction as left ventricular end-diastolic volume fell in most of our patients. Direction calculation of the mean circumferential shortening rate, however, shows a consistent and significant reduction after the drugs. As it seems likely that there will be little change in ventricular structure over a short period, the same fibres may be assumed to occupy a given circumference in the two parts of the study. If the findings are expressed as rate of change in circumference the same effects are evident, offering clear demonstration of a reduction in the velocity of shortening of the individual muscle fibres.

The changes in force and velocity after atropine and propranolol are similar to those which we have reported in other patients with aortic stenosis after propranolol alone (Hamer and Fleming, 1967). The findings are supported by the animal work of Whalen *et al.* (1968) who measured left ventricular volume by cine-angiocardiology in three dogs with surgically induced heart block. The rate was kept constant by pacing, and an increase in left ventricular volume was found after propranolol, though the presence of mitral incompetence in these dogs makes interpretation difficult. Indirect measurements of ventricular performance suggest a

reduction in contractility after propranolol independent of a reduction in heart rate. Bloomfield and Sowton (1967) found a fall in cardiac output and ejection rate in paced patients with heart block, and Shinebourne (1969) showed a similar effect in exercising patients with hypertension at matched heart rates before and after beta-adrenergic blockade.

The reduced velocity of contraction in the absence of any alteration in ventricular wall force indicates a reduction in myocardial contractility. This effect, occurring with an increase in heart rate, cannot be secondary to the negative chronotropic effect of beta-adrenergic blockade, and provides convincing evidence of a negative inotropic effect of propranolol.

SUMMARY

The effect of 5 mg. propranolol on ventricular wall force and velocity of contraction has been studied in 6 patients with severe aortic stenosis at left heart catheterization. The fall in heart rate that is usually produced by propranolol was prevented by giving 2.4 mg. atropine. Force and velocity measurements were based on estimates of left ventricular end-systolic and end-diastolic volume using the thermodilution technique.

Stroke volume and left ventricular ejection rate fell consistently, but there was little change in left ventricular pressures. There was a significant increase in the thermodilution ratio, indicating less complete emptying of the ventricle at each beat, but there was no consistent change in left ventricular end-diastolic volume. Force measurements showed little alteration after propranolol and atropine, but there was a consistent and significant reduction in the mean circumferential shortening rate, indicating a reduction in the velocity of contraction in the left ventricular wall.

The demonstration that 5 mg. propranolol produces a reduced velocity of contraction when the fall in heart rate is prevented by atropine confirms that propranolol diminishes ventricular contractility by a mechanism independent of any reduction in heart rate.

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