J. Physiol. (1973), **235**, *pp.* 571–590
With 8 *text-figures*
Printed in Great Britain

THE MAXIMUM DERIVATIVES OF LEFT VENTRICULAR PRESSURE AND TRANSVERSE INTERNAL DIAMETER AS INDICES OF THE INOTROPIC STATE OF THE LEFT VENTRICLE IN CONSCIOUS DOGS

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(*Received 19 March 1973*)

SUMMARY

1. In normal, conscious dogs, I.V. infusion of isoprenaline caused increases in heart rate and the maximal derivatives of left ventricular pressure (dP/dt max) and left ventricular internal diameter (dD/dt max). The changes in both derivatives were linearly related to the increase in heart rate.

2. Increments in heart rate produced by right atrial pacing caused only minimally significant increases in both dP/dt max and dD/dt max at heart rates of 180 beats/min. Increases in heart rate, with end diastolic diameter maintained constant, resulted in small but significant increases in dP/dt max and no significant increase in dD/dt max.

3. Increasing preload by volume infusion had little effect on either derivative, while increasing afterload by phenylephrine administration produced a small but significant increase in dP/dt max and no change in dD/dt max.

4. Both dP/dt max and dD/dt max are equally reliable as indices of the inotropic state of the myocardium and are minimally influenced by changes in preload, afterload or heart rate.

INTRODUCTION

It is an obvious inference, based on extrapolation from the results of studies of isolated cardiac muscle preparations (Sonnenblick, 1962*a*, *b*), that the rate of tension development and the rate of shortening in the intact left ventricle should provide information about the inotropic state of the myocardium (Reeves, Hefner, Jones, Coghlan, Prieto & Carroll,

1960; Gleason & Braunwald, 1962; Mason, 1969). In the conscious animal, similar data can be obtained by direct measurement of the maximal derivative of the left ventricular pressure (dP/dt max) during 'isovolumic' contraction, and the maximal derivative of the left ventricular internal transverse diameter (dD/dt max) during ejection. However, it has been reported that changes in preload, afterload and heart rate influence these measurements (Reeves *et al.* 1960; Mason, 1969; Wildenthal, Mierzwiak & Mitchell, 1969; Wallace, Skinner & Mitchell, 1963; Wilcken, 1965). If such independent physiological variables substantially affect dP/dt max or dD/dt max, their value as indices of the inotropic state of the cardiac muscle would be limited, except in circumstances where venous return, systemic aortic pressure and heart rate are maintained constant. In addition, in the intact ventricle, dP/dt max and dD/dt max may be influenced by changes in synchronization of contraction (Rushmer, 1956; Randall & Priola, 1965).

Furnival, Linden & Snow (1970) have reported that in open chest, cardiac denervated dogs, changes in preload, afterload and heart rate exert only minimal effects on dP/dt max in comparison with large increases in response to isoprenaline, a positive inotropic agent. In two conscious dogs, Noble, Wyler, Milne & Trenchard (1969) detected no change in dP/dt max during an increase in heart rate. Thus, there have been dissident reports concerning the extent to which haemodynamic changes affect dP/dt max. In addition, there have been no comprehensive efforts to assess the reliability of dD/dt max or related measurements of ventricular muscle shortening as indices to the contractile state of the myocardium.

Accordingly, this study was designed to systematically compare the effect of an inotropic agent with the effects of changes in preload, afterload and heart rate on dP/dt max and dD/dt max in conscious, resting dogs. To accomplish this, the responses to isoprenaline and electrical pacing of the right atrium were compared at a series of matched heart rates. Electrical pacing was performed with both constant and varying preloads. Furthermore, preload and afterload were each independently altered while heart rate was maintained constant.

METHODS

In nine adult mongrel dogs, weighing 16–22 kg, sterile thoractomies were performed under methoxyflurane anaesthesia. Through a stab incision near the apex, a calibrated solid-state pressure transducer (P-18; Konigsberg Instruments) was implanted within the left ventricle. A second stab incision was made through the anterior wall of the left ventricle, and two discoid piezoelectric crystal transducers were inserted using a technique described previously (Horwitz, Bishop, Stone & Stegall, 1968; Bishop, Horwitz, Stone, Stegall & Engelkin, 1969; Bishop & Horwitz,

1971). The transducers were positioned across the greatest internal diameter of the transverse left ventricle, one on the anterior and the other on the posterior endocardial wall. An 18-gauge polyvinyl catheter was placed in the left atrial appendage. The pericardium was left open. The catheter and wires were brought outside the skin at the back of the neck. Two weeks after the thoracotomy, the dogs were again anaesthetized, a 12-gauge polyvinyl catheter was inserted into the left jugular vein and an 18-gauge polyvinyl catheter was inserted into the thoracic aorta via the left common carotid artery. Studies were begun one week after the second surgical procedure. At this time, all animals could exercise normally, and no electrocardiographic abnormalities were present.

Left ventricular transverse internal diameter was obtained with a sonomicrometer (Stegall, Kardon, Stone & Bishop, 1967), which measures the mean transit time for 5 Mc/s ultrasound to traverse the distance between the two piezoelectric crystals. The sampling rate was 5000 times/sec. Left atrial pressure and aortic pressure were measured through the implanted catheter with strain gauge manometers (models P23 BB and Db; Statham Instruments, Inc.) zeroed to the mid line of the sternum while the dog lay on its right side. The solid-state pressure transducers were precalibrated at 38° C and the sensitivity did not change during the implantation, although some drift did occur. On occasion, the left ventricular zero reference was checked with a catheter passed percutaneously into the left ventricle and connected to an external manometer. Since this was not feasible in repeated experiments, the zero reference was corrected by setting the left ventricular end-diastolic pressure equal to the mean left atrial pessure at the beginning of each experiment (Horwitz & Bishop, 1972).

Experimental procedures

Resting measurements were obtained while the animal was lying quietly on its right side, unsedated and lightly restrained. After the control period, one of the following procedures was performed.

Pacing. The heart was electrically paced by passing a no. 5F bipolar pacing catheter into the right atrium via the large catheter in the left jugular vein or by pacing electrodes which were sutured near the sinoatrial node during the initial instrumentation. An electrical stimulator (model S 4; Grass Instrument Co.) was used to pace at 120, 150 and 180 beats/min. Usually, on subsequent days, the response to right atrial pacing was again evaluated during control states when several of the other experimental interventions were evaluated. There was no evidence from the left ventricular internal diameter and pressure recordings that right atrial pacing had an effect on mechanical coupling between the atrium and ventricle.

Pacing with end diastolic diameter constant. End diastolic diameter was maintained constant during right atrial pacing at 120, 150 and 180 beats/min by infusing sterile Ringer solution, which was pre-warmed to body temperature, into the large catheter placed in the left jugular vein. With the fine control of an infusion pump (model RE 161; Holter Co.), the infusion rate could be adjusted so that the end diastolic diameter was maintained constant within $\pm 0{\cdot}1$ mm. Approximately 400 ml. Ringer solution were usually required during this experimental procedure.

Pacing at a constant heart rate during elevations of end diastolic diameter. The heart was electrically paced at 180 beats/min, and end diastolic diameter was increased by rapid I.V. infusion of sterile Ringer solution.

Increased afterload. With heart rate maintained constant by right atrial pacing, aortic pressure was incremented by the I.V. administration of phenylephrine hydrochloride. The dose of phenylephrine was adjusted to obtain the desired aortic pressure (Aviado, 1959).

Positive inotropic and chronotropic changes. In order to obtain steady-state heart rates of 120, 150 and 180 beats/min, an I.V. infusion of isoprenaline hydrochloride was regulated by means of an infusion/withdrawal pump (model 903; Harvard Apparatus Co., Inc.). The infusion rates normally ranged from 0·2 μg/kg per min to 1·1 μg/kg per min.

Statistical analysis. The *t* test was used to evaluate paired observations and the significance of the correlation coefficient (*r*). Linear regression analyses were performed using the least-squares method to determine the equation of the line. In those cases where a significant correlation coefficient existed, analysis of variance was used to determine the S.D. of the slope and the S.D. of the difference between two slopes. The significance of the difference was determined by the *t* test. Analysis of variance was also used to establish the *F* ratio (*F*) to evaluate the linear significance of two variables (Snedecor & Cochran, 1967). *P* values $< 0·05$ were considered significant. A *P* value $< 0·01$ was considered highly significant.

Critique of methods

Based upon its electronic characteristics, the solid-state pressure transducer has a natural frequency in excess of 3000 c/s (Noble, Milne, Goerke, Carlsson, Domenech, Saunders & Hoffman, 1969). The sensitivities of these transducers are stable *in vitro* and *in vivo* (Bishop & Horwitz, 1971; Horwitz & Bishop, 1972); however, significant zero drift may occur (Horwitz & Bishop, 1972). Consequently, an independent zero reference is needed. On occasion, the zero reference, as well as the calibration, were obtained by inserting a catheter into the left ventricle. The catheter manometer- and strain-gauge-measured left ventricular end-diastolic pressure were always within 1·0 mmHg of the left atrial pressure during all states studied. Others have concluded that left atrial pressure is within 0·2 mmHg of the left ventricular end-diastolic pressure (Braunwald & Frahm, 1961). Therefore errors made from setting the left ventricular end-diastolic pressure equal to mean left atrial pressure should not have affected the absolute ventricular pressure by more than 1 mmHg. Therefore, the relative values during an experiment were correct.

The characteristics of the sonomicrometer have been discussed previously (Stegall *et al.* 1967; Horwitz & Bishop, 1972). The theoretical resolution is 0·07 mm at 5 Mc/s. The phase lag of the sonomicrometer is approximately 1·80° per c/s and is linear with frequency; at 20 c/s the amplitude is down 5%. A Fourier analysis of the diameter recording has shown that its frequency components are well described by four harmonics, although twenty harmonics are necessary to describe the pressure wave (Horwitz & Bishop, 1972). Previous studies in this laboratory have confirmed that changes in the transverse internal diameter are a reasonably accurate index of left ventricular volume changes during ejection (Bishop *et al.* 1969; Bishop & Horwitz, 1971; Horwitz & Bishop, 1972).

Analogue derivatives of the pressure and diameter signals were obtained by using active operational amplifier circuits. The amplitude of the differential output was linear from 0·5 to 100 c/s. The output of the operational amplifier was calibrated by differentiating a triangular wave. The relationship of left ventricular pressure and internal diameter to their derivatives is shown in the analogue recording in Fig. 1. All records were read at the time of end expiration after a steady state was achieved; this usually occurred immediately following an intervention and always within 15–30 sec.

RESULTS

In preliminary experiments, we confirmed the finding of Furnival *et al.* (1970) that isoprenaline-induced changes in dP/dt max were not the result of the drug's chronotropic effect since the changes were not altered when the heart rate was kept constant by right atrial pacing. Therefore, we have assumed that, during the infusion of isoprenaline, changes in the chronotropic state are accompanied by proportionate changes in the inotropic state and that dP/dt max is a quantitative index of the inotropic effect of isoprenaline.

TABLE 1. The effects of isoprenaline infusion. E.D.D. = end diastolic diameter; E.S.D. = end systolic diameter; L.V.E.D.P. = left ventricular end-diastolic pressure; M.A.P. = mean aortic pressure; H.R. = heart rate; dP/dt = the maximum rate of change of left ventricular pressure during systole; dD/dt = the maximum rate of change of diameter during ejection. S.E. = the standard error of the mean. $\bar{d}$ (120), $\bar{d}$ (150) and $\bar{d}$ (180) are the mean differences from control during isoprenaline infusion at heart rates of 120, 150 and 180 beats/min, respectively. S.D. is the standard deviation of the mean difference. *, ** and *** = values statistically different from the control at the $P < 0.05$, < 0.01 and 0.001 levels using t test for paired analysis; n = number of animals

	E.D.D. (mm)	E.S.D. (mm)	L.V.E.D.P. (mmHg)	M.A.P. (mmHg)	H.R. (beats/min)	dP/dt (mmHg/sec)	dD/dt (mm/sec)	n
Control								
Mean	37·0	30·1	3·8	100	108	2301	51·3	7
S.E. ±	2·4	2·7	0·6	5	3	159	2·3	
$\bar{d}$ (120)	−0·73**	−1·00**	−1·7*	−2	12**	511**	13·9**	7
S.D. ±	0·15	0·21	0·5	1	2	32	2·5	
$\bar{d}$ (150)	−1·70***	−2·70***	−2·7***	−3*	39***	1099***	26·0***	7
S.D. ±	0·12	0·37	0·3	1	3	85	3·3	
$\bar{d}$ (180)	−2·30***	−3·70***	−3·5***	−5*	70***	1662***	40·3***	7
S.D. ±	0·16	0·56	0·4	2	3	133	4·9	

Intravenous infusion of isoprenaline resulted in substantial, statistically significant increases in dP/dt max and dD/dt max (Table 1, Fig. 2). Plots of the increments in dP/dt max and dD/dt max as a function of the changes in heart rate resulting from the I.V. infusion of isoprenaline are shown in Fig. 3. A significant linear relationship, as indicated by the correlation coefficients and F ratios, existed between the increments in dP/dt max or dD/dt max and the changes in heart rate. dP/dt max increased $19·3 \pm 2·1$ mmHg/sec per beats/min ($r = 0·903$, $F = 84$, $P < 0·001$) and dD/dt max increased $0·42 \pm 0·02$ mm/sec per beats/min ($r = 0·73$, $F = 21$, $P < 0·001$). The percentage increases in dP/dt max and dD/dt max at the highest rate were similar, 72 and 78%, respectively.

As shown in Table 1, left ventricular end diastolic diameter, left ventri-

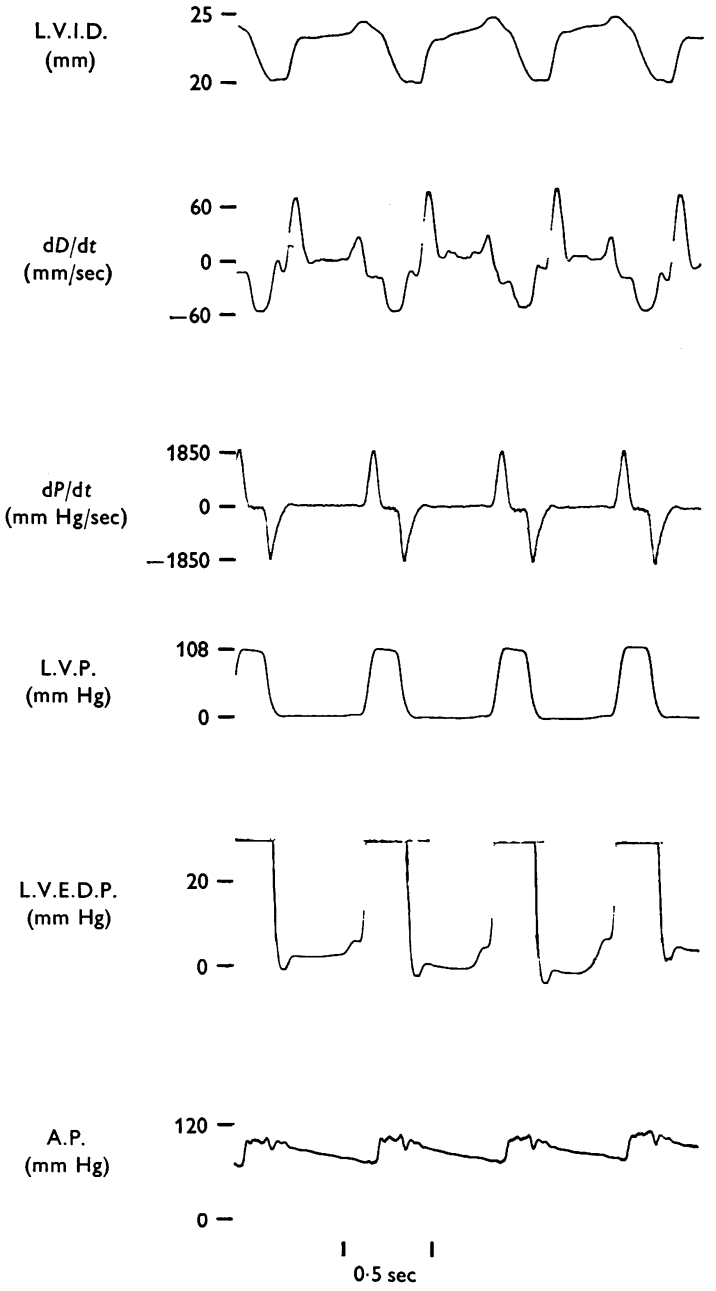

Fig. 1. For legend see facing page.

cular end systolic diameter, and left ventricular end-diastolic pressure decreased as the heart rate increased during intravenous infusion of isoprenaline. The extent of myocardial fibre shortening was increased since the decrement in end systolic diameter was always greater than that observed in end diastolic diameter. The reduction in aortic pressure was minimal.

The response of dP/dt max and dD/dt max to increasing heart rate resulting from right atrial pacing in nine animals is shown in Fig. 4. Increasing heart rate was associated with a linear increase in dP/dt max ($r = 0{\cdot}88$, $F = 82$, $P < 0{\cdot}001$). However, the slope of the relationship ($3{\cdot}03 \pm 0{\cdot}32$ mmHg/sec per beats/min) was only one sixth that observed with similar increments in heart rate resulting from isoprenaline infusion. The difference between the two slopes was significant ($P < 0{\cdot}001$).

Increments in dD/dt max with changes in heart rate by right atrial pacing were less consistent than the changes in dP/dt max. As shown in Table 2, significant increases in dP/dt max and dD/dt max occurred only at the highest heart rates, increasing 7 and 6%, respectively, at heart rates of 180 beats/min.

Elevations of heart rate by right atrial pacing were also accompanied by significant reductions in end diastolic diameter, end systolic diameter and left ventricular end-diastolic pressure (Table 2), while mean aortic pressure was unaffected. The extent of myocardial fibre shortening, as illustrated by the difference in end diastolic and end systolic diameters, was reduced, since increasing heart rate by right atrial pacing resulted in a greater fall in end diastolic than in end systolic diameter.

In five animals the end diastolic diameter was maintained at a constant level during right atrial pacing at heart rates of 120, 150 and 180 beats/min. Under these experimental conditions, the only variable which was significantly altered was dP/dt max which increased 235 mmHg/sec (11%) at the highest heart rate while the change in dD/dt max was 3·9 mm/sec (7·2%) (Table 3). Fig. 5 shows the individual animal responses to right atrial pacing when end diastolic diameter is constant. Inconsistent changes occurred in both dP/dt max and dD/dt max with elevation in heart rate. The largest change in dP/dt max or dD/dt max was small in comparison with those observed with changes in heart rate resulting from isoprenaline infusion.

Fig. 1. An analogue recording obtained from a resting, conscious dog. The simultaneous recordings of left ventricular internal diameter (L.V.I.D.), derivative of left ventricular internal diameter (dD/dt), derivative of left ventricular pressure (dP/dt), left ventricular pressure (L.V.P.), left ventricular end-diastolic pressure (L.V.E.D.P.), aortic pressure (A.P.) and heart rate (H.R.) are shown.

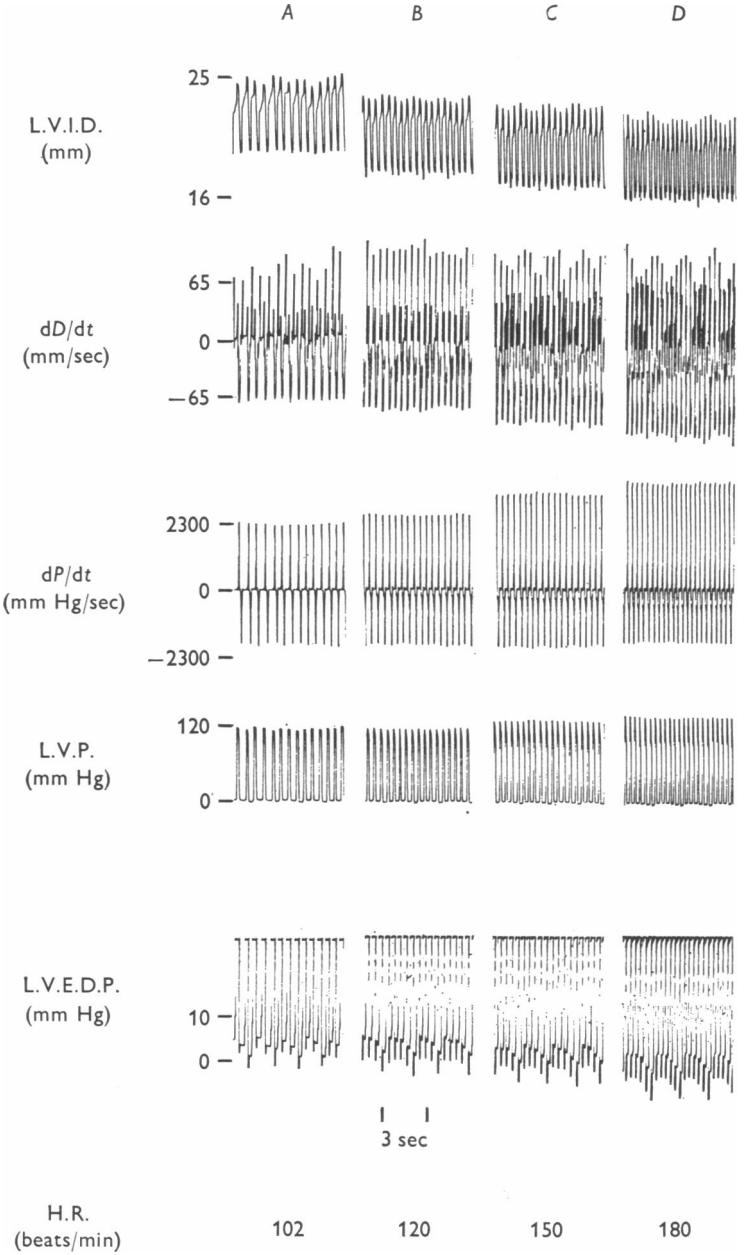

Fig. 2. An analogue recording obtained during continuous infusion of isoprenaline. Control recording is shown below panel *A*. The effects of the continuous infusion of isoprenaline are shown below panels *B*, *C* and *D*. Note the progressive increases in (−) d*D*/d*t* and (+) d*P*/d*t* during the administration of isoprenaline.

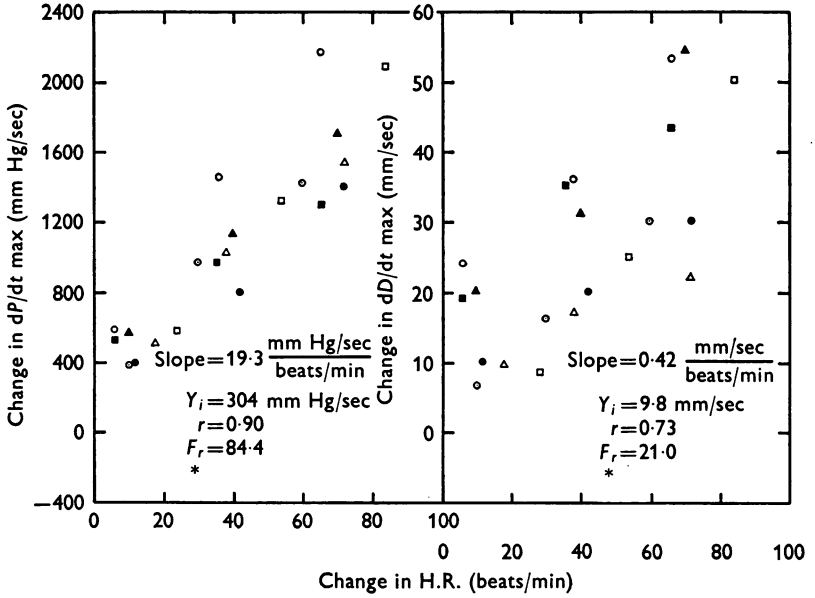

Fig. 3. The relationship between changes in heart rate and changes in dP/dt max and dD/dt max during isoprenaline infusion in seven dogs. Each symbol represents results obtained in one dog. * = $P < 0{\cdot}001$ for both r and F. Y_i = Y intercept.

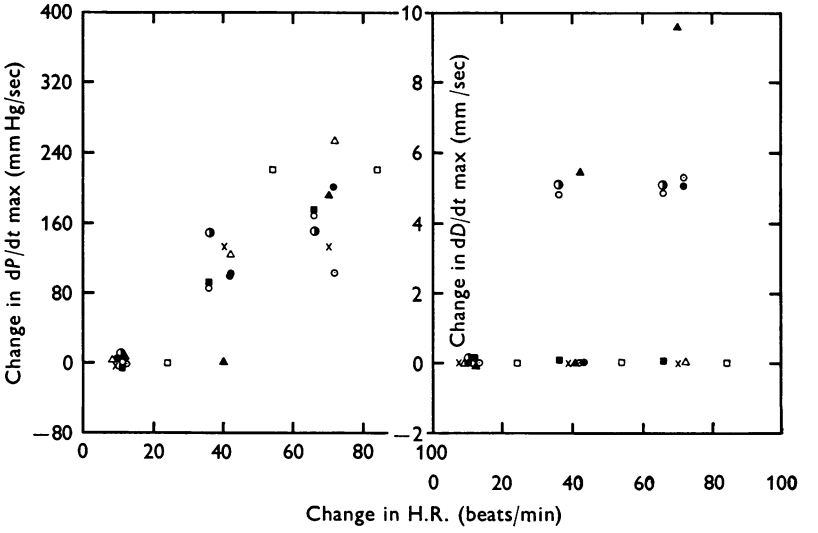

Fig. 4. The effect of changes in heart rate by right atrial pacing on dP/dt max and dD/dt max in nine dogs. Each symbol represents results obtained in one dog.

Heart rate was controlled at 180 beats/min in four animals while end-diastolic diameter was continuously elevated by I.V. infusion of Ringer solution (Fig. 6). Table 4 shows the mean changes resulting from this procedure. Only end diastolic and end systolic diameters and left ventricular end-diastolic pressure were significantly elevated. At the greatest end diastolic diameter, similar increases occurred in dP/dt max (8%) and dD/dt max (10%).

TABLE 2. Effects of changes in heart rate by right atrial pacing. $\bar{d}$ (120), $\bar{d}$ (150) and $\bar{d}$ (180) are the mean differences from control during right atrial pacing at heart rates of 120, 150 and 180 beats/min, respectively. Abbreviations are the same as in Table 1

	E.D.D. (mm)	E.S.D. (mm)	L.V.E.D.P. (mmHg)	M.A.P. (mmHg)	H.R. (beats/min)	dP/dt (mmHg/sec)	dD/dt (mm/sec)	n
Control								
Mean	37·6	30·3	3·8	101	108	2372	53·5	9
S.E. ±	2·4	2·5	0·6	5·0	2	148	2·4	
$\bar{d}$ (120)	−0·23***	−0·23**	−0·3*	0·3	12***	0	0	9
S.D. ±	0·07	0·07	0·1	0·9	2	0	2	
$\bar{d}$ (150)	−1·17***	−0·67***	−1·2*	2·2	40***	101**	1·7	9
S.D. ±	0·13	0·10	0·4	1·0	2	23	0·8	
$\bar{d}$ (180)	−2·17***	−1·12***	−2·4**	2·3	70***	176***	3·3*	9
S.D. ±	0·17	0·06	0·5	1·0	2	15	1·2	

TABLE 3. Effects of changes in heart rate by right atrial pacing (E.D.D. constant). $\bar{d}$ (120), $\bar{d}$ (150) and $\bar{d}$ (180) are the mean differences from control during right atrial pacing with E.D.D. maintained constant by rapid I.V. infusion of Ringer solution into the right atrium. Abbreviations are the same as in Table 1

	E.D.D. (mm)	E.S.D. (mm)	L.V.E.D.P. (mmHg)	M.A.P. (mmHg)	H.R. (beats/min)	dP/dt (mmHg/sec)	dD/dt (mm/sec)	n
Control								
Mean	40·6	33·8	6·4	91	107	2143	53·8	5
S.E. ±	3·6	3·5	2·6	7·4	4	228	4·3	
$\bar{d}$ (120)	−0·00	−0·16	0·4	0·8	13*	89**	1·5	5
S.D. ±	0·25	0·09	0·3	0·5	4	17	1·0	
$\bar{d}$ (150)	0·14	0·08	1·6	2	43***	150**	2·9	5
S.D. ±	0·55	0·24	1·6	1	4	17	1·2	
$\bar{d}$ (180)	−0·11	−0·04	1·6	4	73***	235*	3·9	5
S.D. ±	0·60	0·16	1·8	2	4	60	1·8	

Increases in aortic pressure with a constant heart rate resulted in significant increments in end diastolic and end systolic diameters, left ventricular end-diastolic pressure and dP/dt max (Table 5). However, with a change in mean aortic pressure of 48 mmHg, dP/dt max was

increased only 9%, while a slight reduction in dD/dt max was not statistically significant. Fig. 7 illustrates the changes in dP/dt max and dD/dt max as a function of the change in aortic pressure. Although the correlation coefficient is small, a linear relationship appears to exist for changes in dP/dt max ($r = 0{\cdot}56$, $P < 0{\cdot}05$). As indicated by the slopes of the curves ($4{\cdot}27 \pm 1{\cdot}88$ mmHg/sec per mmHg and $-0{\cdot}06 \pm 0{\cdot}02$ mm/sec

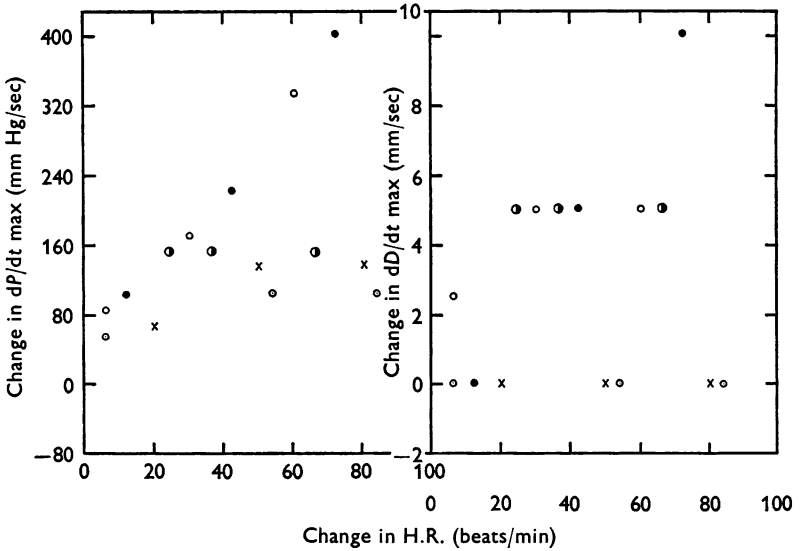

Fig. 5. The effect of changes in heart rate by right atrial pacing (with end diastolic diameter maintained constant) on dP/dt max and dD/dt max in five dogs. Each symbol represents results obtained in one dog.

TABLE 4. Effects of changes of E.D.D. at a constant heart rate. Heart rate was maintained at 180 beats/min by right atrial pacing. P-180 indicates pacing at 180 beats/min. $\bar{d}$ is the mean difference from control during changes in E.D.D. by rapid I.V. infusion of Ringer solution into the right atrium. Abbreviations are the same as in Table 1

	E.D.D. (mm)	E.S.D. (mm)	L.V.E.D.P. (mmHg)	M.A.P. (mmHg)	dP/dt (mmHg/sec)	dD/dt (mm/sec)	n
Control, P-180							
Mean	32·5	27·1	2·8	96	2340	54·9	4
S.E. ±	3·6	3·8	0·6	8·0	157	2·1	
$\bar{d}$	0·75*	0·40*	1·3*	1·6	25	0	4
S.D. ±	0·16	0·08	0·2	1·6	25	0	
$\bar{d}$	1·55*	1·07*	3·5*	5·2	50	1·2	4
S.D. ±	0·32	0·30	0·8	2·1	50	1·2	
$\bar{d}$	2·80*	1·60*	6·5**	8·1	181	5·2	4
S.D. ±	0·63	0·42	0·8	3·1	86	2·0	

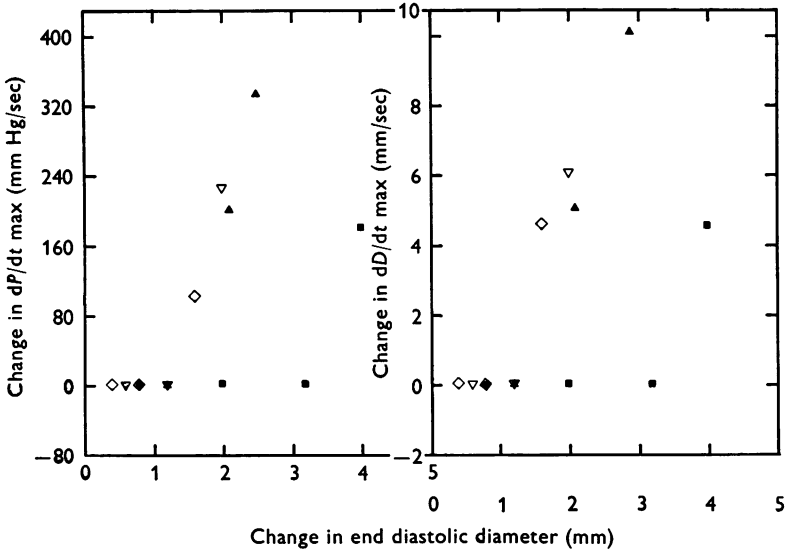

Fig. 6. The effect of increments in end diastolic diameter on dP/dt max and dD/dt max in four dogs. Heart rate maintained constant. Each symbol represents results obtained in one dog.

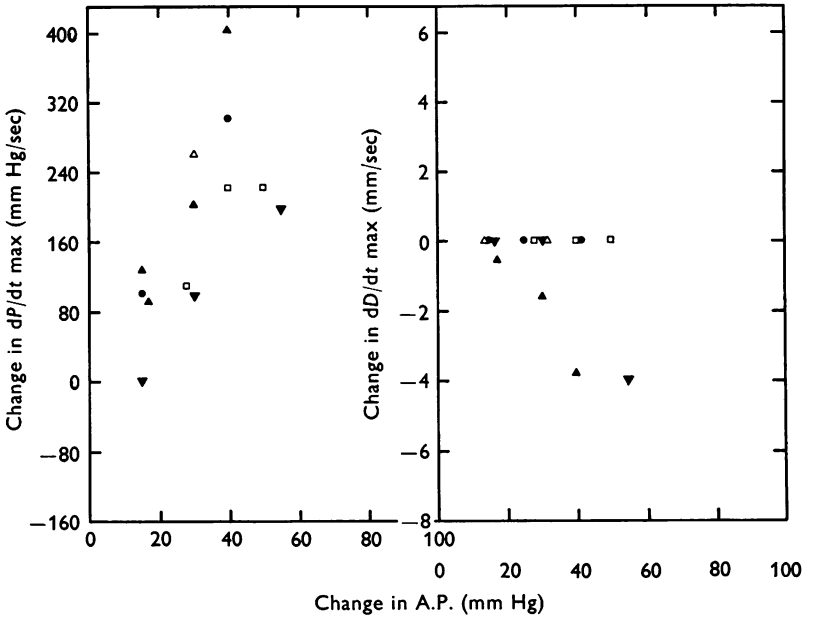

Fig. 7. The effect of changes in aortic pressure on dP/dt max and dD/dt max in five dogs. Heart rate maintained constant by right atrial pacing. Each symbol represents results obtained in one dog.

TABLE 5. Effects of changes in aortic pressure at a constant heart rate. Heart rate was maintained constant by right atrial pacing. $\bar{d}$ is the mean difference from control during changes in aortic pressure. Abbreviations are the same as in Table 1

	E.D.D. (mm)	E.S.D. (mm)	L.V.E.D.P. (mmHg)	M.A.P. (mmHg)	dP/dt (mmHg/sec)	dD/dt (mm/sec)	n
Control							
Mean	30·3	21·9	4·0	98	2561	57·6	5
S.E. ±	0·3	2·1	0·7	3	155	1·9	
$\bar{d}$	0·66*	0·58**	3·0*	17**	108*	−0·1	5
S.D. ±	0·20	0·09	0·8	3	32	0·1	
$\bar{d}$	1·64*	1·68*	5·6**	33***	234**	−0·7	5
S.D. ±	0·57	0·56	1·1	3	49	0·7	
$\bar{d}$	1·86*	2·2*	9·3**	48**	237**	−1·3	4
S.D. ±	0·52	0·41	1·6	4	33	1·3	

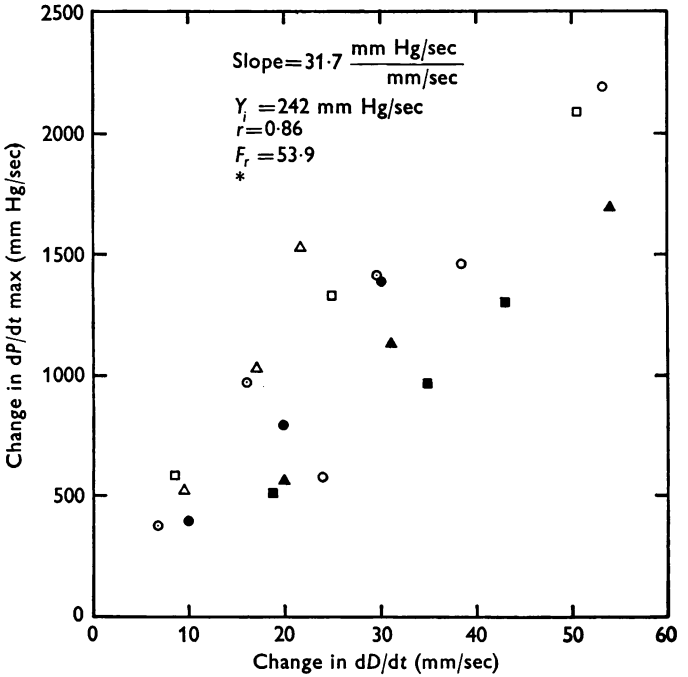

Fig. 8. The relationship between the changes in dP/dt max and dD/dt max during infusion of isoprenaline (data obtained from ordinates of Fig. 3). * = $P < 0{\cdot}001$ for both r and F.

per mmHg), changes in mean aortic pressure in the physiological range have only minimal effects on dP/dt max and dD/dt max.

The values represented as the ordinates in Fig. 3 were replotted in Fig. 8 to demonstrate the relationship between the change in dP/dt max and dD/dt max. This relation was clearly linear ($r = 0{\cdot}86$, $F = 54$, $P < 0{\cdot}001$). The slope ($31{\cdot}7 \pm 4{\cdot}4$ mmHg/sec per mm/sec) is a function of the absolute units in which each derivative is measured. When the percent changes rather than the absolute units were compared, the sensitivities of the two variables were found to be similar.

DISCUSSION

Quantification of the contractile properties of the myocardium is a highly desirable, but extremely complex, endeavour. Hill (1938) described skeletal muscle contraction in terms of velocity of shortening and developed force. Attempts have been made to apply his mode to cardiac muscle (Sonnenblick, 1962*a*, *b*; Abbott & Mommaerts, 1959). This has involved the concept of a contractile element which shortens and develops force, and is in series with a passive elastic element. An increase in contractility has been described as an increase in the maximum velocity of shortening of the contractile element; it has been proposed that this parameter is a fundamental property of cardiac muscle and is independent of preload or afterload. In the intact heart, left ventricular end-diastolic pressure is the analogue of preload, and aortic systolic ejection pressure reflects the initial afterload (Sonnenblick *et al.* 1962*a*, *b*).

However, particularly in the intact heart, application of the force–velocity relationship to cardiac muscle has important limitations (Parmley, Yeatman & Sonnenblick, 1970; Pollack, 1970). The active state, during which force is exerted, is inconstant in its time course and is slower to develop in cardiac than in skeletal muscle (Brady, 1968). Therefore, measurements obtained at different times in the cardiac cycle, and under varying conditions, may reflect different intensities of the active state. The relatively high resting tension of cardiac muscle and the probable presence of viscous and inertial elements are not adequately accounted for by a two-element model (Parmley *et al.* 1970; Pollack, 1970). A serious objection is that the cardiac force–velocity relationship does not always appear to be hyperbolic. Also, accurate extrapolation to a theoretical maximum velocity of contractile element shortening at zero load is difficult (Brady, 1968; Noble, Bowen & Hefner, 1969). Furthermore, recent studies have demonstrated that the force–velocity relationship is not independent of preload (Noble *et al.* 1969; Donald, Unnoppetchara, Peterson & Hefner, 1972).

For the above reasons, the maximum velocity of contractile element shortening cannot be interpreted as a fundamental property of cardiac muscle, but rather an index to changes in contractility or the inotropic state. Inasmuch as maximum contractile element velocity is a theoretical concept which is based on questionable assumptions, we have investigated the value of the directly measured parameters from which it is derived, dP/dt max and dD/dt max, as indices of the inotropic state of the myocardium.

To a limited extent, both of these derivatives have previously been utilized in this fashion. Frank (1895) and Wiggers (1914) recognized the dependence of the rate of rise of the left ventricular pressure upon the inotropic state of the myocardium. Others have reported that catecholamines increase dP/dt max and circumferential shortening rate, which is dD/dt max multiplied by a constant (Gleason & Braunwald, 1962; Franklin, Van Citters & Rushmer, 1962; Glick, Sonnenblick & Braunwald, 1965; Sonnenblick, Braunwald, William & Glick, 1965; Gorlin, Rolett, Yurchak, Elliott, Lane & Levy, 1964; Rushmer & West, 1957). Several studies have concluded that dP/dt max is determined by the contractile element velocity and the stiffness of the series elastic element (Sonnenblick, 1964; Levine & Britman, 1964; Ross, Covell, Sonnenblick & Braunwald, 1966). In addition, Levine & Britman (1964) found that, during maximum left ventricular ejection, contractile element velocity and circumferential shortening rates were similar.

Thus, it may be inferred from previous work that dP/dt max, during 'isovolumic' systole, and dD/dt max, during peak ejection, are functions of the contractile element velocity and are indices of the inotropic state of the myocardium. However, to some extent, changes in dP/dt max and dD/dt max may be influenced by alterations in the synchrony of contraction during the pre-ejection and ejection phases of systole (Rushmer, 1956; Priola, Osadjan & Randall, 1965; Szentivanyi, Pace, Wechsler & Randall, 1967; Jóhannsson & Nilsson, 1972). In addition, the practical usefulness of dP/dt max and dD/dt max for this purpose has been uncertain because the degree to which preload, afterload or heart rate influences them has not been delineated. Although a number of reports have indicated that these variables affect the magnitude of dP/dt max (Reeves *et al.* 1960; Gleason & Braunwald, 1962; Mason, 1969; Wildenthal *et al.* 1969; Wallace *et al.* 1963; Ross *et al.* 1966; Siegel & Sonnenblick, 1963; Mitchell, Wallace & Skinner, 1963), a recent investigation in denervated, open chest dogs found no consistent changes in response to increases in preload and only minimal changes due to increases in heart rate (Furnival *et al.* 1970).

Our study represents the first systematic effort to precisely determine

the extent of the individual and collective effects of changes in heart rate, preload and afterload on dP/dt max and dD/dt max in conscious, resting animals. By use of high-fidelity, instantaneous recordings of left ventricular pressure and transverse internal diameter, processed with active electronic differentiators, we have obtained more reliable measurements than those obtained by previous studies of intact hearts. This is particularly true of studies in which circumferential shortening was indirectly estimated from indicator-dilution data (Gorlin *et al.* 1964) or calculated from external dimension records (Glick *et al.* 1965; Rushmer & Smith, 1959). Indirect measurements require assumptions and are not instantaneous. Since the myocardial muscle mass is constant throughout the cardiac cycle, thickening of the left ventricular wall occurs as the muscle fibres shorten (Feigl & Fry, 1964). Therefore, differentials of external dimension measurements will be substantially less in magnitude than differentials of internal dimensions measurements and will seriously underestimate muscle fibre and contractile element shortening by a variable and unpredictable amount. On the other hand, the differential of the internal diameter may over-estimate the rate of myocardial fibre shortening. However, for the above reasons, changes in this variable are more easily interpreted in terms of myocardial mechanics.

Isoprenaline markedly increased dP/dt max, dD/dt max and the extent of myocardial fibre shortening in all animals. As the rate of the infusion was increased, the inotropic response paralleled the chronotropic response, and both derivatives increased linearly with heart rate. Although the increases in dP/dt max and dD/dt max are primarily due to an increase in the inotropic state of the myocardium, the changes could be partially influenced by isoprenaline-induced alterations in synchrony of muscular contraction. There is a lack of data to ascertain the extent to which this could be a factor (Priola *et al.* 1965; Szentivanyi *et al.* 1967; Jóhannsson & Nilsson, 1972).

Augmentation of heart rate by right atrial pacing with varying or constant preload had only small effects on dP/dt max and dD/dt max. Afterload was not altered under these conditions. The Bowditch staircase effect, whereby increasing the frequency of stimulation increases the contractile force, has been reported in isolated hearts and in intact, anaesthetized animals (Bowditch, 1871; Woodworth, 1902; Blinks & Koch-Weser, 1963). However, this phenomenon could not be consistently demonstrated in conscious dogs or humans by other investigators (Noble *et al.* 1969; Gault, Ross & Braunwald, 1968).

Increments in the initial fibre length (end diastolic diameter) with heart rate constant also resulted in small increases in dP/dt max and dD/dt max. Increases in dP/dt max in response to initial fibre stretch have

been reported by a number of investigators (Reeves *et al.* 1960; Wallace *et al.* 1963; Siegel & Sonnenblick, 1963). However, critical analysis of their data suggests that there were inconsistencies in the occurrence and magnitude of the positive inotropic effect.

In our study, increments in aortic pressure, although reducing the extent of myocardial fibre shortening, increased dP/dt max only slightly while dD/dt max was essentially unchanged. Since the baroreceptor reflex was intact in these conscious animals, sympathetic withdrawal probably occurred (Lindgren & Manning, 1965). The maintenance of dD/dt max, despite sympathetic withdrawal, apparently resulted from the direct inotropic effect of the increasing aortic pressure (Clancy, Graham, Ross, Sonnenblick & Braunwald, 1968) or from an increase in preload resulting in the operation of the Frank–Starling mechanism.

In the normal conscious dog, both dP/dt max and dD/dt max are equally sensitive to positive inotropic changes as indicated by their response to isoprenaline. Contrary to previous studies, neither of these indices was sensitive to alterations in initial fibre length, aortic pressure or heart rate. Since the peak ejection rate of the left ventricle occurs before the peak tension (Ross *et al.* 1966) and the maximum rate of myocardial fibre shortening, as indicated by dD/dt max, corresponds to the peak ejection rate (Bishop & Horwitz, 1971), the effects of afterload on dD/dt max are minimized. Therefore, both dP/dt max, a measurement obtained during 'isovolumic' systole, and dD/dt max, a measurement obtained during peak ejection, were reliable indices of the inotropic state. The use of these two indices may provide insight into the relationship between the properties of the heart muscle and its function as a pump.

Since these experiments were performed in normal hearts, additional information is needed to evaluate the sensitivity and selectivity of dP/dt max and dD/dt max as indices of the inotropic state in diseased or depressed hearts. It is conceivable that the influence of preload or afterload may be increased under such conditions. This would explain some of the variation in the results of other studies, although Furnival *et al.* (1970) found that dP/dt max was only minimally altered by preload and afterload in an open chest, presumably depressed, preparation.

We would like to acknowledge the excellent surgical and technical assistance of Miss Linda Fox and Mr Ben Wiggins. Supported in part by the National Institutes of Health Grant HL12415, Air Force Contract No. AFOSR-71-2074, and the Texas Heart Association.

This research is part of a dissertation thesis presented to the faculty of the graduate programme of the University of Texas Medical School at San Antonio in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Pharmacology.

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