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LEFT VENTRICULAR MECHANORECEPTORS: A HAEMODYNAMIC STUDY

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SUMMARY

1. To study the function of the left ventricular mechanoreceptors, a working left ventricle preparation was devised in dogs which permitted control of pressure and flow of the isolated perfused coronary circulation and of the flow of the isolated, separately perfused systemic circulation. The systemic circulation was perfused at a constant rate so that changes in systemic pressure reflected changes in systemic resistance.

2. Increases in myocardial contractility produced by injection of catecholamines into the isolated, perfused coronary circulation produced a fall in the pressure (resistance) of the isolated, separately perfused (at a constant rate) systemic circulation.

3. Completeness of isolation of the coronary and systemic circulations was shown by the marked difference in appearance times between the reflex hypotensive responses from catecholamine injections into the isolated coronary circulation and the direct hypertensive response from a similar injection when the circulations were connected as well as by the marked difference between the pressure pulses recorded simultaneously on both sides of the aortic balloon separating the two circulations.

4. Myocardial β receptor blockade produced by injection of propranolol into the isolated coronary circulation abolished or attenuated the changes in left ventricular myocardial contractility as well as the subsequent hypotensive responses following the similar injection of catecholamines.

5. Electrical stimulation of a sympathetic nerve innervating the heart resulted in increases in left ventricular myocardial contractility and subsequent systemic hypotensive responses indistinguishable from those following injection of catecholamines.

6. That distortion of the mechano- or stretch receptors in the left ventricular myocardium was the cause of the hypotensive responses was demonstrated by increasing left ventricular myocardial contractility by mechanically obstructing the left ventricular outflow which produced

hypotensive responses similar to those following the injection of catecholamines or nerve stimulation.

7. Bilateral high cervical vagotomy abolished the hypotensive responses following injection of catecholamines into the isolated coronary circulation or following left ventricular outflow obstruction in all but one instance, indicating the importance of vagal fibres to the afferent arm of the reflex.

8. It is suggested that the left ventricular mechanoreceptors function normally to reduce the peripheral resistance in order to prepare the systemic circulation to receive the left ventricular output and, especially during exercise, to prepare the systemic circulation to receive the augmented cardiac output with a minimum alteration in the systemic blood pressure and to distribute this augmented output preferentially to the skeletal muscles.

INTRODUCTION

A reflex initiated by mechanoreceptors (stretch or baroreceptors) located in the left ventricle which produces systemic hypotension has been studied in dogs, cats, rabbits, frogs, and chickens (Daly & Verney, 1927; Kolatat, Kramer & Mühl, 1957; Aviado & Schmidt, 1959; Salisbury, Cross & Rieben, 1960; Coleridge, Coleridge & Kidd, 1964; Pillsbury, Guazzi & Freis, 1969; Oberg & Thoren, 1972; Estavillo & Burger, 1973). A major site of the vasodilator response has been localized to skeletal muscles (Mark, Abboud, Schmid, Heistad & Johannsen, 1973), the afferent path to the vagus (Daly & Verney, 1927; Kolatat *et al.* 1957; Pillsbury *et al.* 1969; Oberg & Thoren, 1972; Estavillo & Burger, 1973; Mark *et al.* 1973; Linden, 1973; Shepherd, 1973) and premature ventricular contractions have been implicated in the initiation of the reflex (Ross, Frahm & Braunwald, 1961). Nerve recordings in vagal fibres and also localization of the site of the receptors in the myocardium by their response to punctate stimulation have been carried out (Coleridge *et al.* 1964; Sleight & Widdicombe, 1965; Muers & Sleight, 1972). Paintal (1955, 1973) concluded that the reflex is due to receptors having an early systolic discharge and which are not localized to the epicardium. Haemodynamic changes similar to those of the left ventricular mechanoreceptor reflex have been shown to result from the coronary chemoreflex (Dawes & Comroe, 1954) and from the epicardial chemoreflex (Sleight & Widdicombe, 1965; Bergel & Makin, 1967).

In a previous study from this laboratory (Chevalier, Weber, Lyons, Nicoloff & Fox, 1974) stimulation of the left ventricular mechanoreceptors was produced by sudden distension with saline of an intraventricular balloon. This led to a fall in systemic resistance and often bradycardia in the pneumonectomized dogs in which the systemic circulation was isolated

from the non-working heart by constant-rate, retrograde perfusion via total cardiac by-pass. Left atrial and right ventricular pressures were unchanged and the pericardium had been removed, eliminating any role receptors in those chambers or in the pericardium might play in the result. It was suggested that the reflex which is initiated in the heart, in addition to peripheral effects, also acts on the heart itself to regulate myocardial contractility, in addition to altering the heart rate. The reflex nature of the systemic vasodilatory response was assumed from the time course and other characteristics of the response since, contrary to earlier findings (Daly & Verney, 1927; Aviado & Schmidt, 1959; Doutheil & Kramer, 1959; Salisbury *et al.* 1960; Mark *et al.* 1973), bilateral high cervical vagotomy usually only attenuated but did not abolish the response. Thus, in addition to the vagus nerves, the afferent arm of this reflex was also felt to be carried, to a greater or lesser extent, in spinal afferent fibres for which some evidence has been obtained (Khabarova, 1963; Hess, Zuperku, Coon & Kampine, 1974; Weaver, 1976).

Next we studied these left ventricular receptors, whose response to mechanical stimuli and/or intraventricular pressure elevation had been documented by recording from vagal A-δ and C fibres *in vivo* (Paintal, 1955; Coleridge *et al.* 1964) or post-mortem (Coleridge *et al.* 1964; Sleight & Widdicombe, 1965; Muers & Sleight, 1972), in a manner analogous to that used to study the carotid sinus mechanoreceptors, namely by passively distending with a saline-filled balloon the fibrillating, perfused left ventricular wall of pneumonectomized dogs on cardiac by-pass (Leonard, Einzig, Nicoloff & Fox, 1975). As in the case of studies in the isolated carotid sinus, the magnitude of the systemic pressure fall increased with increasing rate of distension of the fibrillating left ventricle and the plot of the left ventricular distending pressure versus the resultant decrease in the systemic arterial pressure (resistance) yielded the sigmoid curves characteristic of the isolated carotid sinus preparation (Heymans & Neil, 1958; Kirchheim, 1976).

It had been noted in the course of our investigation that even gently touching the beating or fibrillating left ventricular wall (pericardium removed) produced a systemic hypotensive response in dogs on cardiac by-pass at constant-rate systemic perfusion. Because of the complex structure of the left ventricular wall compared to that of the carotid sinus, the former being composed of differently oriented layers of striated muscle which contract during systole, it is unlikely that either intraventricular balloon distension or external manual compression of the left ventricle represents a physiological stimulus to the mechanoreceptors in its wall. Nonetheless, since, like mechanoreceptors elsewhere in the body, the left ventricular mechanoreceptors could be expected to be stimulated by

distortion whether or not it is physiologically applied, the effect on the systemic arterial pressure of controlled, external manual compression (Paintal, 1955) of the asystolic, unperfused (aorta ligated) left ventricle preparation from which the right ventricle, left atrium and pericardium had been removed was compared to that of controlled distension of the isolated carotid sinuses (Moissejeff preparation) (Leonard, Einzig, Gerasch, Nicoloff & Fox, 1976). Either gentle (barely altering intraventricular pressure) or forceful, external manual compression of the asystolic, unperfused left ventricle onto an intraventricular saline-filled balloon produced a typical systemic hypotensive response in the pneumonectomized dogs on cardiac by-pass at constant-rate systemic perfusion, the magnitude of the hypotensive response being roughly proportional to the compressive force as measured by the rise in the intraventricular pressure. Furthermore, especially in the physiological blood pressure range of between 80 and 140 mmHg, when manual left ventricular compression onto an intraventricular saline-filled balloon was added to carotid sinus distension to the same pressure level, there was a significantly greater decrease in the systemic perfusion pressure than when the carotid sinuses were distended alone to this pressure.

To produce a more physiological stimulus, a new preparation was devised in which both the coronary circulation and the systemic circulation are isolated and perfused at a constant rate via separate pump-oxygenator circuits (Fig. 1). It was reasoned that if the left ventricular mechanoreceptors behaved like stretch receptors elsewhere in the body (muscle spindles, Golgi tendon organs, carotid sinuses, (Bronk & Stella, 1935; Heymans & Neil, 1958; Henneman, 1974)), they should respond to changes in the rate and force of contraction of the left ventricular myocardium produced by catecholamines. In accordance with our self-imposed constraint to produce physiological stimulation, minimal effective stimuli were used throughout this study.

METHODS

Under chloralose (100 mg/kg) anaesthesia dogs immobilized with gallamine triethiodide (3 mg/kg) were placed on total cardiopulmonary by-pass, pneumonectomized and the pericardium removed. The systemic and coronary circulations were separated by passage into the ascending aorta via a left ventricular apical stab wound, secured by purse-string sutures, of the tip of a closed-ended balloon catheter (6–8 mm internal diameter) and inflation of its terminal balloon just above the coronary ostia. A catheter was positioned in the left atrium at the mitral valve to permit infusion of blood into the beating left ventricle for ejection by the latter into the coronary circulation. Large side holes in the left ventricular portion of the aortic balloon catheter permitted an alternate route of egress for the left ventricular ejectate, namely via the apical end of the aortic catheter which was connected to

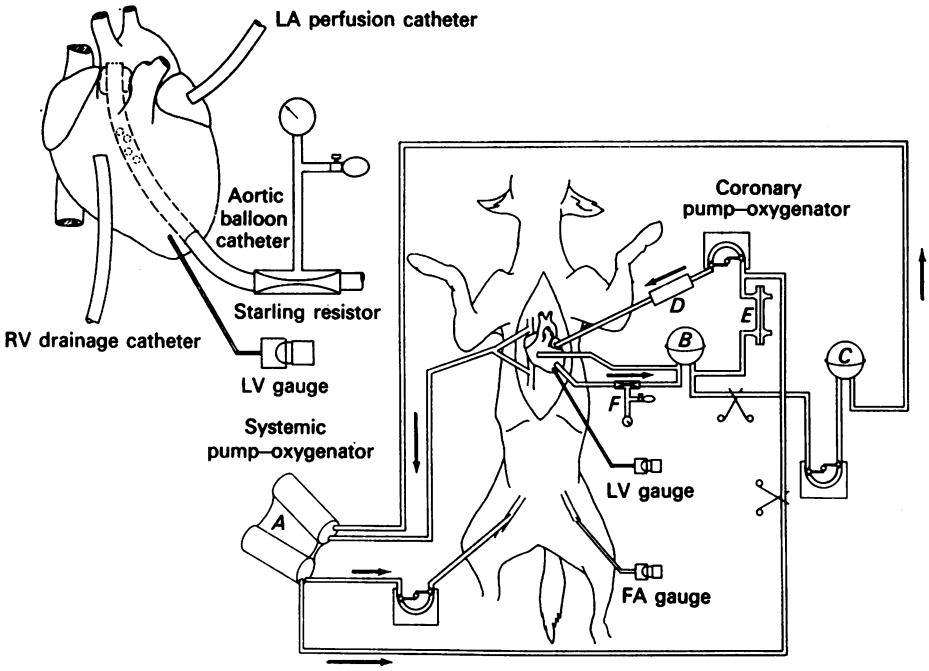

Fig. 1. Assembly for isolation of and controlling perfusion rate and pressure of the coronary circulation of a working left heart preparation and for isolation of and controlling perfusion rate of the systemic circulation of a pneumonectomized dog on total cardiac by-pass (pericardium removed). For isolation of the coronary and systemic circuits, aortic catheter balloon is inflated just above coronary ostia (see insert) and perfusion lines are clamped at the location of forceps. *A*, bubble oxygenator (100 % O_2), heat exchanger and reservoir of systemic circuit. *B*, reservoir of coronary circuit. *C*, blood filter used when systemic and coronary circuits are connected. *D*, membrane oxygenator (100 % O_2) of coronary circuit. *E*, heat exchanger of coronary circuit. *F*, Starling resistor assembly (see insert) permitting control of pressure against which working left ventricle perfuses the coronary circulation. Insert shows enlarged view of connexions to heart. Aortic balloon catheter, with balloon inflated just above coronary ostia, has large side holes in its left ventricular portion permitting beating left ventricle to eject varying proportions of its stroke volume into coronary ostia and out apical end of catheter, the proportion of blood passing in each direction being controlled by pressure in Starling resistor. Right ventricular drainage catheter also permits measurement of coronary flow. Coronary circulation is perfused antegradely by left ventricle which receives blood via atrial perfusion catheter; systemic circulation is perfused retrogradely via femoral artery catheter; systemic venous drainage is via superior and inferior caval catheters, as shown. Femoral arterial and left ventricular catheters are attached to strain-gauge manometers for pressure measurement.

a Starling resistor by means of which the pressure under which the coronary arteries were perfused by the beating left ventricle, i.e. the left ventricular afterload could be controlled (see insert Fig. 1). The coronary venous return (coronary sinus plus right ventricular luminal) was drained into a reservoir via a catheter in the right ventricle. Thus, a working left ventricular preparation was achieved in which both the coronary perfusion pressure and coronary flow could be controlled while in the separately perfused systemic circulation the systemic flow could be controlled and kept constant so that changes in systemic pressure reflected changes in systemic resistance.

The tip of a no. 6 F standard catheter was advanced into the descending thoracic aorta via the left femoral artery while the tip of a no. 7 F standard catheter was advanced into the left ventricle via the apical stab wound and both catheters were connected to strain-gauge manometers (Statham P23 De and P23 Gb respectively) for pressure measurement. The sensitivity of the aortic pressure manometer was 100 mm Hg/50 mm. All pressures (aortic, aortic mean, left ventricular) were referred to mid-chest level and, along with the left ventricular dP/dt (differentiating circuit) and e.c.g. were recorded on a photo-oscillograph (Honeywell Visicorder Model 1012) which permitted visual monitoring of the pressures so that manoeuvres could be performed when the mean aortic pressure was constant (flat).

Both circulations were perfused at a constant rate with fresh heparinized donor dog blood (22 m-equiv $NaHCO_3$ added to perfusate/30 min), mean values for the blood pH of 7·51 (range 7·39–7·65), for the P_{O_2} of $>$ 300 mmHg, for the P_{CO_2} of 14 (range 2–34) mmHg and for the haematocrit of 33 (range 25–44) % being obtained in the left atrial perfusion line in five dogs having these determinations during the experiments, data from three of which being included in this study. To minimize the occurrence of ventricular premature contractions, lidocaine (80–100 mg) was injected into the isolated coronary circulation in three animals which produced no apparent changes in the hypotensive responses under study. As a test of the integrity of the carotid sinus reflex arc, the common carotid arteries were occluded near the end of the experiment in most animals and the expected reflex systemic hypertension was obtained in every instance.

Nine dogs with a mean control systemic arterial pressure of 74 ± 3 (S.E. of mean; range 65–90) mmHg and a mean heart rate of 147 ± 9 (range 114–180) beats/min and mean systemic and left atrial perfusion rates of $66 \pm 4{\cdot}1$ (range 48–81) ml./kg.min and $13 \pm 1{\cdot}6$ (range 5–19) ml./kg.min respectively, form the basis of this study.

RESULTS

Infusion into the isolated coronary circulation of small doses of noradrenaline, adrenaline, or isoprenaline produced the expected increase in myocardial contractility, e.g. an increase in left ventricular peak dP/dt accompanied by an increased left ventricular systolic pressure and usually a decreased left ventricular diastolic pressure which was associated with an increase in the heart rate as is seen in Fig. 2. and Table 1. This increase in contractility, which was proportional to the dose of drug injected, resulted in a mean fall of 23 % in the pressure, i.e. a decrease in the resistance of the separately perfused (at constant rate) and completely isolated systemic circulation, the magnitude of the systemic arterial pressure fall in a particular animal being roughly proportional to the degree of increase

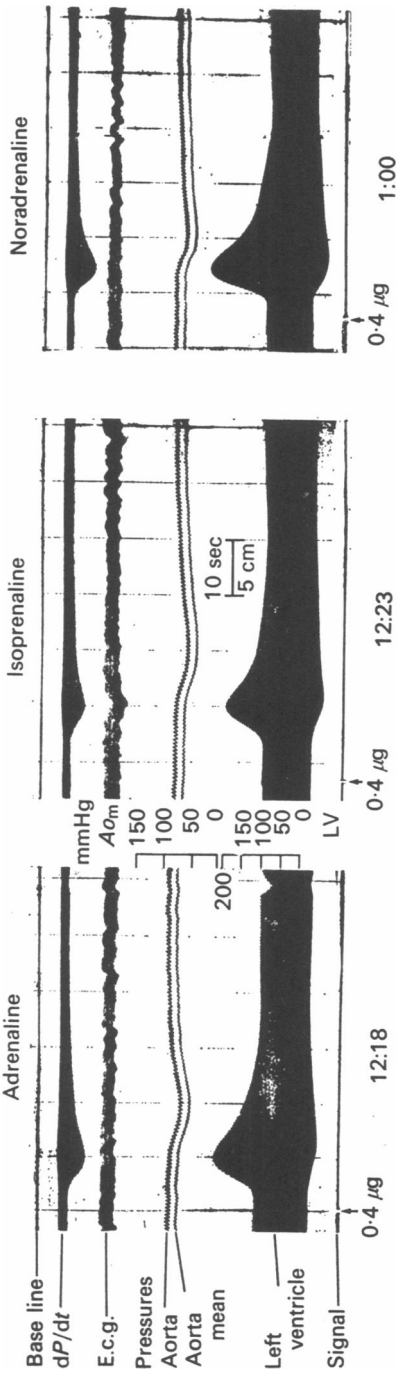

Fig. 2. Original recordings showing comparison of effect of successive injections of similar doses (0·4 μg) of adrenaline, isoprenaline, or noradrenaline into the isolated coronary circulation of the same dog, pneumonectomized and on total cardiac by-pass at constant-rate systemic perfusion. Note increases in left ventricular (LV) systolic pressure and peak dP/dt and decreases in left ventricular diastolic pressure as evidence of increased myocardial contractility which is followed by a fall in the mean aortic pressure (Ao_m) of the isolated, separately perfused systemic circulation. Coronary and systemic circulations connected between injections to minimize build-up of drug concentrations in coronary circulation as evidenced by similarity of the control deflexion of the LV peak dP/dt in all three records. Times of injections (at signal) are given.

TABLE 1. Effect of injection of catecholamines into the isolated, perfused coronary circulation on the contractility of the left ventricle and on the mean aortic pressure of the isolated and separately perfused (at constant rate) systemic circulation

Drug	Number of observations	Dose (μg)	Control mean aortic pressure (mmHg)	Change in mean aortic pressure (% of control)	Change in LV peak dP/dt (% of control)	Change in LV systolic pressure (% of control)	Change in heart rate (% of control)
Noradrenaline	22 (8)*	0·144 ± 0·15† (0·001 to 0·4)	73 ± 3·2 (53 to 105)	−25 ± 2·6 (−2 to −38)	278 ± 40 (30 to 611)	104 ± 14 (9 to 274)	32 ± 6·4 (0·5 to 125)
Adrenaline	16 (6)	10·14 ± 6·76‡ (0·001 to 100)	66 ± 2·9 (54 to 100)	−23 ± 3·7 (−4 to −52)	193 ± 58 (9 to 700)	84 ± 23 (4 to 305)	30 ± 5·2 (0·to 67)
Isoprenaline	8 (5)	0·178 ± 0·08 (0·008 to 0·4)	64 ± 6·6 (50 to 103)	−22 ± 4·2 (−4 to −37)	159 ± 62 (22 to 550)	56 ± 14 (9 to 103)	19 ± 7·0 (0 to 60)

* The number in parentheses denotes number of animals in which observations were made.

† ± S.E. of mean.

‡ Note all doses were 0·4 μg or less except three doses in one animal which was less sensitive to the drug.

in contractility, as is seen in Fig. 3. The time from the onset of the increase in myocardial contractility (peak dP/dt) to the maximal aortic pressure fall averaged $14 \pm 0{\cdot}6$ s.

Minimum increases in the left ventricular peak dP/dt and systolic pressure of 9 and 4% of their control values respectively were associated with a definite hypotensive response (at least a 2 mmHg change if the mean aortic pressure was flat and a > 5 mmHg difference between the response and fluctuations in the control pressure, if present), but increases in both of these indices of myocardial contractility always preceded the hypotensive responses. In the total of forty-six observations following catecholamine injections which were included in this study, that is, observations with stable pressures during the control period, without the occurrence of arrhythmias and which were made at a time when the animal's haemodynamic status as judged by the level of the mean aortic and left ventricular systolic, diastolic and pulse pressures, was satisfactory, there was not a single instance in which a measurable hypotensive response was not obtained.

Completeness of the isolation of the systemic and coronary circuits was evidenced by the marked difference between the appearance times of the reflex hypotensive and of the direct hypertensive systemic pressure responses, 13–15 sec *vs.* 74 sec respectively, to injections of catecholamines at approximately the same location with the two circulations isolated in the former case and connected in the latter case in which a massive dose of 5 mg adrenaline was injected at the end of the experiment to rule out leaks. In addition, the marked difference in the pressure pulse contours recorded simultaneously on both sides of the aortic balloon (see Fig. 3) is further evidence for the isolation of the two circuits since the aortic catheter lay just downstream to the balloon.

To determine whether the peripheral vasodilation produced by the injection of the catecholamines into the isolated coronary circulation was actually the result of the increase in myocardial contractility which these compounds apparently cause by stimulation of the myocardial β receptors, β receptor blockade was produced by administration of propranolol (0·1–0·5 mg) into the isolated coronary circulation in five dogs. Depending on the degree of blockade which it produced, propranolol, which decreased myocardial contractility (decreased peak dP/dt, increased left ventricular diastolic pressure (see Fig. 4)), either completely abolished (Fig. 4) or attenuated the expected increase in myocardial contractility and the subsequent fall in the systemic arterial pressure following the injection of isoprenaline or adrenaline, known β receptor stimulators, in all nine observations in the five dogs. The increase in myocardial contractility and the subsequent systemic arterial pressure fall following noradrenaline,

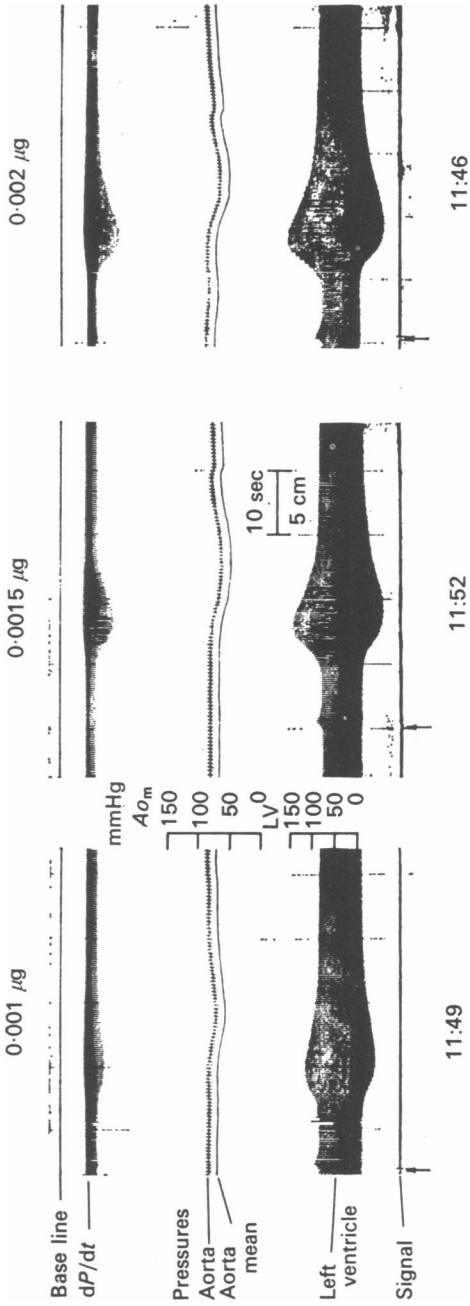

Fig. 3. Original recordings showing injection in rapid succession of increasing doses of noradrenaline into the isolated coronary circulation of the same pneumonectomized dog on total cardiac by-pass at constant-rate systemic perfusion. Note that with progressively increasing drug dose there is evidence of progressively increasing myocardial contractility (increasing magnitude of LV peak dP/dt, LV systolic pressure rise and increasing diastolic pressure fall) which is followed by a progressively increasing fall in the mean aortic pressure (Ac_m) of the isolated, separately perfused systemic circulation. Coronary and systemic circulations connected between injections (see legend of Fig. 2). Times of injection (at signal) are given.

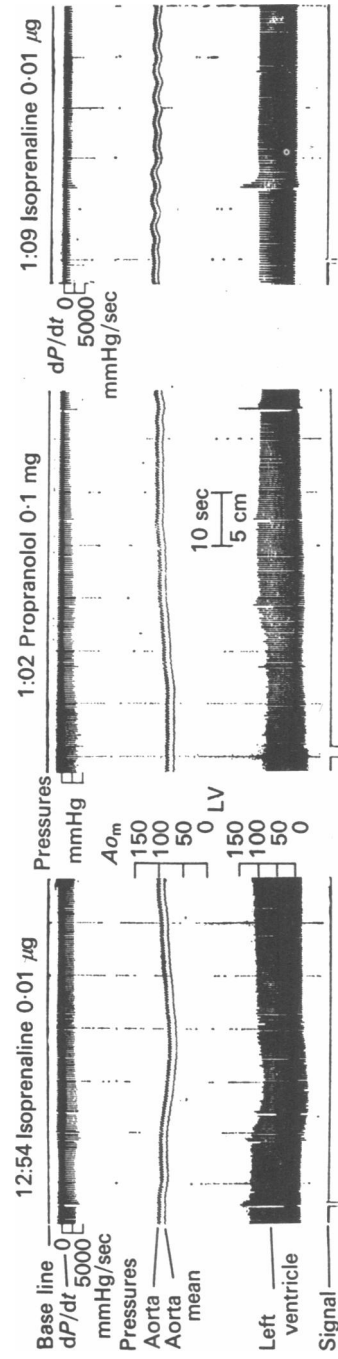

Fig. 4. Original recordings showing comparison of effect of injections of similar doses of isoprenaline (0·01 μg) into the isolated coronary circulation of the same dog, pneumonectomized and on total cardiac by-pass at constant-rate systemic perfusion, before (left panel) and after (right panel) injection of 0·1 mg propranolol into the isolated coronary circulation (centre panel). Note first, the absence of the typical rise in left ventricular systolic pressure and in peak dP/dt (an artifact is present in these, however) and of the subsequent fall in the mean aortic pressure (Ao_m) of the isolated, separately perfused systemic circulation following the injection of isoprenaline after propranolol (right panel) while these are present before propranolol (left panel). Note also (centre panel) the decrease in the left ventricular peak dP/dt and the increase in the left ventricular diastolic pressure, both evidence of a decrease in myocardial contractility, after the injection of propranolol. The subsequent increase in the mean aortic pressure after propranolol seen in this dog (centre panel) was not a consisent finding. Coronary and systemic circulations connected between injections (see legend of Fig. 2). Times of injection (at signal) are given.

believed to be primarily an α but also a β receptor stimulator (Viveros, Garlick & Renkin, 1968), were abolished after propranolol in five observations in two dogs and unaltered in three observations in two other dogs, the doses of noradrenaline in the latter animals, however, being at or near the maximum used in this study.

Furthermore, to show that mechanical distortion of the receptors is the cause of the systemic hypotensive response, as would be expected if stretch or mechanoreceptors in the left ventricular wall are the receptors for the reflex, the left ventricular outflow resistance was suddenly elevated by increasing the pressure in the Starling resistor. As is seen in Fig. 5 and Table 2, this resulted in an increase in left ventricular myocardial contractility as evidenced by a mean increase in left ventricular peak dP/dt and systolic pressure of 103 ± 17 (range 15–256) and 77 ± 13 (range 12–250)% respectively, and subsequent systemic hypotensive responses averaging 23 % of control pressure which, depending on the degree to which the left ventricular outflow resistance was increased, resembled the hypotensive responses following various doses of the catecholamines both in their time course and magnitude. Contrariwise, subsequent reduction of the increased left ventricular outflow resistance back toward control level (Fig. 5 and Table 2) with its associated decrease in myocardial contractility (decreased peak dP/dt and decreased left ventricular systolic pressure of $-41 \pm 5{\cdot}5$ and $-33 \pm 4{\cdot}2$ %, respectively) resulted in a $26 \pm 4{\cdot}3$ (range 4–76)% increase in the mean aortic pressure above the minimum pressure level reached during the manoeuvre in nineteen observations in six dogs.

To rule out the possibility that pressure changes stimulating mechanoreceptors in the short segment of the ascending aorta isolated along with the left ventricle in our preparation (see Fig. 1, insert) could be the cause of the hypotensive response, the effect of inflation of the aortic balloon on the systemic arterial pressure was examined and in eight observations in seven dogs a rise in the systemic arterial pressure of $17 \pm 5{\cdot}5$ (range 0–41) %, which is the opposite of the fall in pressure which would be expected from stimulation of aortic receptors, was obtained.

Finally, because it was felt to be more physiological than drug administration and to resemble more closely the situation in the intact animal, electrical stimulation (20 V, 15 c/s, 1·5 msec duration pulses) of the ventrolateral cervical cardiac nerve, a sympathetic nerve (possibly with some parasympathetic fibres (Armour, Hageman & Randall, 1972)) innervating the heart almost exclusively (Mizeres, 1955), was used to increase myocardial contractility. In twenty observations in three dogs, typical systemic hypotensive responses averaging $18 \pm 1{\cdot}3$ (range 8–30)% of control were produced by such stimulation which increased myocardial contractility as evidenced by increases in left ventricular peak dP/dt of

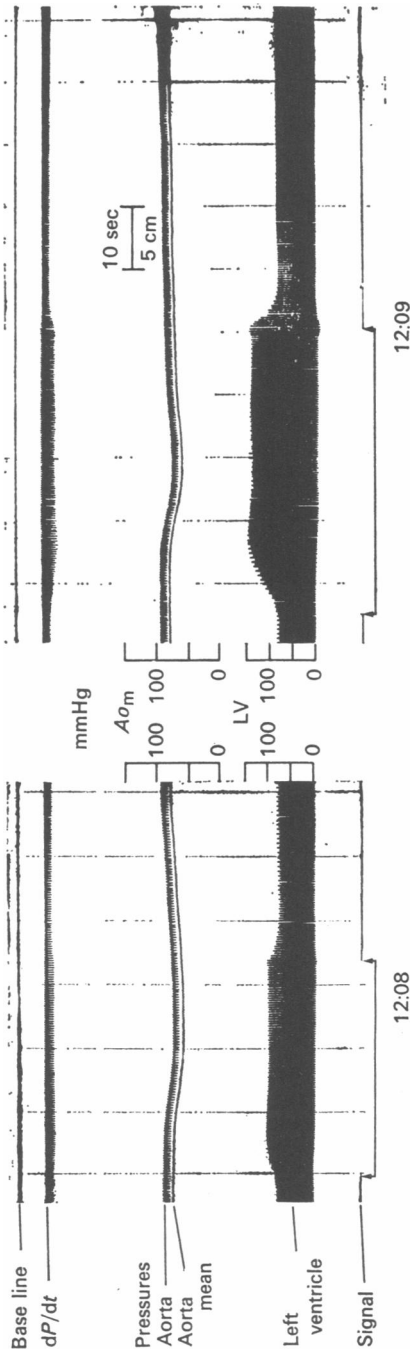

Fig. 5. Original recordings showing effect of successively increasing and decreasing the degree of left ventricular outflow obstruction by changing pressure in Starling resistor on the mean aortic pressure (Ao_m) of separately perfused, isolated systemic circulation of pneumonectomized dog, on total cardiac by-pass at constant-rate systemic perfusion. Left panel: raising pressure in Starling resistor (at first arrow), which increased LV systolic pressure from 80 to 103 mmHg and was associated with a minimal increase in LV peak dP/dt, caused a fall in mean aortic pressure of 21 % below the control pressure of 75 mmHg. Subsequently lowering the pressure in the Starling resistor (at second arrow), decreased the LV systolic pressure from 103 to 80 mmHg while returning the LV peak dP/dt toward control level and raising the mean aortic pressure 32 % above the minimal level reached in the manoeuvre at the peak of the mean aortic pressure (which is off the record to the right). Right panel: similarly raising LV systolic pressure (at first arrow) from 80 to 144 mmHg which was associated with a moderate increase in LV peak dP/dt caused a fall in mean aortic pressure of 24 % below the control pressure of 78 mmHg. Subsequent, similar lowering of the LV systolic pressure (at second arrow) from 144 to 80 mmHg while returning the LV peak dP/dt to control, raised the mean aortic pressure 37 % above the minimal level reached in the manoeuvre at the peak of the mean aortic pressure (which is off the record to the right).

TABLE 2. Effect of increasing and decreasing left ventricular outflow obstruction by changing pressure in Starling resistor on left ventricular systolic pressure and contractility in isolated, perfused coronary circulation and on mean aortic pressure of the isolated and separately perfused (at constant rate) systemic circulation

Manoeuvre	Number of observations	Control LV systolic pressure (mmHg)	LV systolic pressure level reached (mmHg)	Control mean aortic pressure (mmHg)	Change in mean aortic pressure (% of control)	Change in LV peak dP/dt (% of control)	Change in LV systolic pressure (% of control)	Change in heart rate (% control control)
Increased LV outflow obstruction	20 (7)*	87 ± 7·6† (34 to 180)	141 ± 8·0 (87 to 210)	68 ± 2·9 (48 to 100)	−23 ± 2·3‡ (−8 to −43)	103 ± 17·0 (15 to 256)	77 ± 12·9 (12 to 250)	5 ± 2·6 (−13 to 37)
Decreased LV outflow obstruction toward control level	19 (6)	138 ± 7·8 (87 to 210)	92 ± 8·4 (60 to 190)	51 ± 2·9 (36 to 82)	26 ± 4·3§ (4 to 76)	−41 ± 5·5 (−7 to −85)	−33 ± 4·2 (−6 to −68)	−3 ± 2·7 (−30 to 25)

* The number in parentheses denotes number of animals in which observations were made.

† ± S.E. of mean.

‡ Pressure changes are in per cent of control pressure before obstruction.

§ Pressure changes are in per cent of minimal pressure level reached in the manoeuvre (see legend of Fig. 5).

106 ± 15 (range 50–317)% and in the left ventricular systolic pressure of 48 ± 3 (range 28–78)% (Fig. 6), the magnitude of the hypotensive response again being roughly proportional to the increase in contractility in a particular animal.

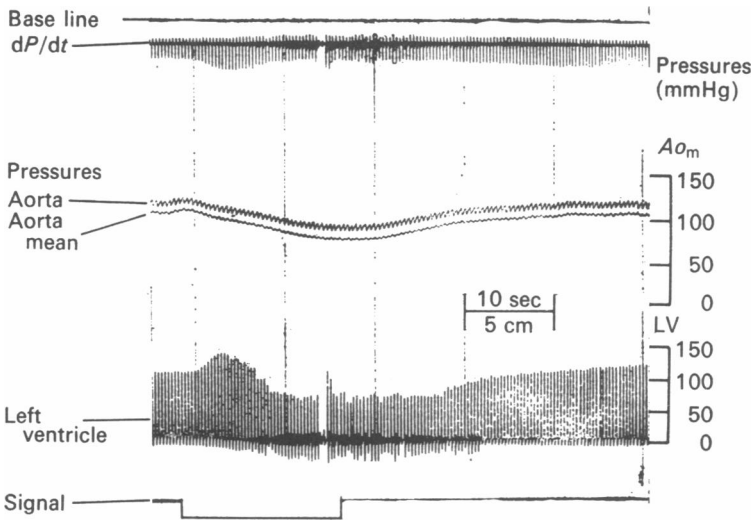

Fig. 6. Original recording showing effect of electrical stimulation (20 V, 15 c/s, 1·5 msec duration pulses) of ventrolateral cervical cardiac nerve in a pneumonectomized dog on total cardiac by-pass at constant-rate systemic perfusion. Note the increase in LV myocardial contractility (increase in LV peak dP/dt and systolic pressure and decrease in LV diastolic pressure) following electrical stimulation (at signal) which produced a 30% fall in the mean aortic pressure (Ao_m) of the separately perfused, isolated systemic circulation. Initial rise in left ventricular systolic pressure is followed by a fall in this pressure below control presumably because the constant left atrial perfusion rate is unable to keep up with the increased left ventricular ejection.

In four of five animals which underwent bilateral high cervical vagotomy, 0·01–0·4 μg doses of noradrenaline which produced a typical hypotensive response before vagotomy (mean -21% of control systemic pressure) failed to produce a response in three of the animals and produced a minimal response (-5%) in the remaining animal, the maximum interval between the observations made before and after vagotomy being 20 min. In the remaining animal in which a comparison of the response to catecholamines before and after vagotomy was not made, left ventricular outflow obstruction which produced a mean systemic pressure fall of 34% of control in four observations before vagotomy, failed to produce a hypotensive response following vagotomy, the maximum interval between

observations made before and after vagotomy also being 20 min. In the one dog in which this was tried, vagotomy abolished the effect of ventrolateral cervical cardiac nerve stimulation.

DISCUSSION

The common mechanical factor underlying the reflex systemic hypotensive responses elicited in the present experiments in a working left ventricle preparation by such disparate stimuli as (1) injection of catecholamines into the isolated coronary circulation, (2) left ventricular outflow obstruction and (3) cardiac sympathetic nerve stimulation is believed to be the increase in myocardial contractility which was associated with all of our effective stimuli. Further evidence for this conclusion comes from the finding that the systemic hypotensive responses produced by spontaneously occurring premature ventricular contractions were also accompanied by an increase in left ventricular myocardial contractility as well as the finding that the magnitude of the systemic hypotensive responses was roughly proportional to the increase in myocardial contractility produced by the initiating stimulus, regardless of its nature.* The fact that the prior injection of propranolol abolished the hypotensive responses following the injection of the catecholamines into the isolated coronary circulation only in those instances in which the catecholamines failed to produce an appreciable increase in myocardial contractility (peak dP/dt) whereas the hypotensive responses persisted in those instances in which the catecholamines continued to produce an appreciable increase in myocardial contractility after propranolol is further evidence for the role of the increase in myocardial contractility in producing the hypotensive response. Finally, in our previous studies in the beating, non-working heart (Chevalier *et al.* 1974), balloon distension of the left ventricle was invariably followed by very forceful contractions which caused an almost threefold increase in the left ventricular systolic pressure, evidence that an increase in myocardial contractility most likely played a role in initiating the hypotensive responses in these experiments also.

It is well known that mechanoreceptors are exquisitely sensitive to the rate of change of the applied distortion, as from the increase in myocardial contractility produced by the above-named stimuli, as well as being sensitive to the distortion itself, as produced by balloon distension or manual compression of the fibrillating or of the unperfused, asystolic left ventricle in our earlier experiments. The fact that simply increasing the

* This conclusion is further supported by the finding that the onset of the increase in myocardial contractility preceded the onset of the fall in the systemic arterial pressure by a mean value of 4.1 ± 0.4 sec ($P < 0.01$).

rate of distension of the wall of the fibrillating, perfused left ventricle nearly doubled the magnitude of the hypotensive responses as well as the ability to elicit hypotensive responses, similar in all respects to those from the foregoing stimuli, by manual compression of the unperfused, asystolic left ventricle in our earlier experiments (Leonard *et al.* 1975, 1976) and of the perfused, working left ventricle of the present study make it highly likely that we are dealing with left ventricular mechano- or stretch receptors and not chemoreceptors in our present as well as our earlier studies.

Determination of the appropriate, physiological stimulus to the left ventricular mechanoreceptors is made difficult by the complex structure and contractile nature of the left ventricle as compared to the carotid sinus, but, on the basis of our results, the sensing of the rate of change of myocardial contraction could fulfil this role, which would depend on the location of the receptors and their connexions within the myocardium. While these mechanoreceptors have been suggested (Jarisch & Richter, 1939; Ross *et al.* 1961; Bergel & Makin, 1967) to sense ventricular filling primarily, this conflicts with the finding that receptors responding to changes in left ventricular pressure discharge early in systole, during the isometric phase of ventricular contraction (Paintal, 1955). The effectiveness of the administration of the physiological neurotransmitter substance solely to the myocardium and of the stimulation of sympathetic nerves whose distribution is localized to the myocardium in eliciting the reflex hypotensive response in the present study strongly suggest that neural mechanisms may be involved in the physiological stimulus to the left ventricular mechanoreceptor reflex.

The time course and magnitude of the systemic vasodilatory response from injection of the catecholamines into the isolated coronary circulation in the present experiments were similar to those previously obtained with balloon distension, e.g. the time from the onset of the increase in contractility (dP/dt) to the nadir of the 23 % systemic pressure fall of 14 sec compares closely to the value of 12 sec for the interval from the rise of the left ventricular pressure to the maximum systemic pressure fall of 27 % following balloon distension (Chevalier *et al.* 1974).

Vagal fibres would appear to play a more important role in carrying the afferent impulses of the left ventricular mechanoreceptor reflex than earlier findings from this laboratory (Chevalier *et al.* 1974) would indicate, vagotomy having abolished the reflex in four of five dogs and markedly attenuated it in the remaining dog in the present study, which could be due to differences between the animal preparations or between the stimuli used to elicit the reflex in the different studies. The importance of these differences to the results obtained may be ascertained from the fact that the large changes in the systemic blood volume of animals on

cardiopulmonary by-pass as a result of stimulation of the left ventricular mechanoreceptors reported by others (Salisbury *et al.* 1960; Ross *et al.* 1961) have never occurred in our experiments.

All of our animals were studied in the presence of active sino-aortic mechanoreceptors so that the hypotensive responses, i.e. decreases in systemic resistance all are of lower magnitude than would be expected if the sino-aortic mechanoreceptors were denervated or the carotid sinuses isolated and perfused at a constant pressure within the physiological range (80–140 mmHg) at which our previous work has shown the responses of the left ventricular and carotid sinus mechanoreceptors to be additive (Leonard *et al.* 1976). As in the case of the balloon distension or manual compression in our earlier fibrillating or asystolic left ventricular preparations (Leonard *et al.* 1975, 1976), the hypotensive responses to the more physiological stimuli of the present study were relatively brief (see Figs. 2, 5, 6) which we attribute to the action of the sino-aortic mechanoreceptors, initially overridden by the reflex, in returning the systemic pressure towards normal. The intactness of the carotid sinus reflex arc, verified in our preparation, would support this contention. Regarding the effect of general anaesthesia on our results, it is not unreasonable to assume that the ventricular and sino-aortic mechanoreceptor reflexes would be similarly depressed by the anaesthetic so that more marked responses from release of either of these reflexes could be expected in the intact, unanaesthetized animal.

From our results, the most important function of the left ventricular mechanoreceptors, because of their cyclic stretching and unloading by each heart beat, would appear to be the reduction of the peripheral resistance in order to prepare the systemic circulation to receive the left ventricular stroke volume with a minimum alteration in the systemic arterial pressure. In support of this suggestion one may cite the finding that the left ventricular mechanoreceptors discharge before the sino-aortic mechanoreceptors (Paintal, 1955). This reduction in resistance would be expected to be a cumulative effect rather than a beat-by-beat fluctuation of the resistance as evidenced by our previous finding (Leonard *et al.* 1976) that cyclic compression of the asystolic left ventricle, in the presence of the sino-aortic mechanoreceptors, was able to maintain systemic hypotension throughout the 30 sec period over which this was studied. In addition to the results of the present study, previous experiments from this laboratory (Leonard *et al.* 1976) in which global infarction and the induction of asystole in the beating, non-working heart by ligation of the root of the aorta in pneumonectomized animals on by-pass, at constant-rate systemic perfusion and with the left atrium, right ventricle and pericardium excised, caused a $19{\cdot}0 \pm 9\%$ rise in the systemic arterial

pressure ($P < 0{\cdot}01$) over a 10 min period, a pressure rise which was probably attenuated by the effects of anaesthesia, would also support this conclusion that the left ventricular mechanoreceptors produce significant inhibition of the vasomotor centres. This function of the left ventricular mechanoreceptors would appear to be most important in exercise, beginning with the 'anticipatory response' (Uvnäs, 1960). Based on the results of the present experiments, the increased left ventricular myocardial contractility under these circumstances can be expected to set in motion the mechanoreceptor reflex permitting the systemic vascular bed to receive the increased cardiac output without an undue and deleterious rise in the systemic arterial blood pressure and, since skeletal muscle vessels appear to be preferentially involved in the response (Viveros *et al.* 1968; Mark *et al.* 1973; Tuttle & Moe, 1973), as in the epicardial chemoreflex (Bergel & Makin, 1967), to effect a redistribution of the increased cardiac output which is appropriate to exertion. The importance of this function to the body's homeostatic mechanisms may be ascertained from the fact that this reflex has been shown previously, as in the present study, to override the sino-aortic mechanoreceptor reflex (Salisbury *et al.* 1960; Chevalier *et al.* 1974), and yet the two may be considered as working in concert to maintain the systemic arterial pressure constant.

The location of the left ventricular mechanoreceptors in the myocardium assures their stimulation prior to opening of the aortic valve which would admirably suit the function of preparing the systemic bed for receipt of the left ventricular stroke volume whereas the sino-aortic mechanoreceptors, stimulated after those in the left ventricle, may form a secondary control mechanism to maintain the systemic arterial pressure. Also their location directly in the cyclically contracting left ventricular myocardium permits the left ventricular mechanoreceptors to sense the rate and force of myocardial contraction immediately at the time the force is generated and thus, by means of neural feed-back mechanisms to the heart, to actively control the development of the pressure by the left ventricle for perfusing the systemic circulation. In addition, in conjunction with the sino-aortic mechanoreceptors and their neural feed-back mechanisms, they may regulate, by neural mechanisms, the perfusing pressure and the distribution of the blood flow to the particular vascular beds in the systemic circulation.

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