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The effects of pronethalol and propranolol on the coronary circulation of the dog

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1. The actions of pronethalol and propranolol have been studied to see if there was any relationship between the reduction in coronary flow and any other cardiovascular action they have.

2. The experiments were carried out in anaesthetized open chest dogs. Measurements included central arterial, left and right venous or atrial pressures, heart rate, ventricular size and stroke volume, intra-ventricular pressures, total left coronary flow, arterial and coronary sinus blood pO_2. The pressure-time index (PTI) and maximum rate of isovolumetric contraction (dp/dt) were obtained from these records.

3. It was concluded that, in these experiments, the reduction in coronary flow produced by pronethalol and propranolol was not directly related to a decrease in perfusion pressure, a raised venous pressure, the increase in ventricular volume and hence wall tension, the decrease in heart rate, or to the increased duration of systole.

4. The PTI and dp/dt were always reduced at the same time as the coronary flow. These findings are discussed.

5. Studies of the effects of sympathetic stimulation, of phentolamine, of reduced arterial oxygen tension and electrical pacing of the heart, all after β-blockade, did not support the suggestion that the reduction in coronary flow after β-blockade was due to the unmasking of an active vasoconstriction.

Bilateral upper sympathectomy produces an objective improvement in selected patients with refractory anginal pain (Apthorp, Wedgewood & Heyward, 1960; Apthorp, Chamberlain & Heyward, 1964). When the β-adrenoceptor blocking agents pronethalol and propranolol became available it was shown that these produced a similar increase in effort tolerance and in the effort electrocardiogram of patients with angina pectoris (Alleyne, Dickinson, Dornhorst, Fulton, Green, Hill, Hurst, Laurence, Pilkington, Prichard, Robinson & Rosenheim, 1963; Chamberlain & Howard, 1964). The improvement in the effort electrocardiogram provided objective evidence suggesting that after the β-adrenoceptor blocking agents the heart

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was no longer suffering an oxygen deficiency. This effect could arise by two mechanisms. Either the compounds could produce a dilatation of the coronary vessels and so increase the oxygen available to the myocardium, or they could reduce the oxygen demand to a value the coronary circulation could supply. It was quickly apparent that pronethalol and propranolol did not produce a dilatation of the coronaries in experimental animals, but rather a constriction. Therefore the mechanism of this constriction and of any concurrent change in oxygen demand became of primary interest. Many factors have been postulated as modifying coronary flow (Gregg & Fisher, 1963), and most of them are altered by β-adrenoceptor blocking agents. An attempt has been made to investigate the influence of these factors in reducing coronary flow following pronethalol and propranolol, and also to investigate an aspect of the problem expressed by Parratt & Grayson (1966). They suggested that these compounds might remove the vasodilatation mediated through the β-adrenoceptors and so unmask a vasoconstrictor response mediated through the α-adrenoceptors, with a risk of severe myocardial anoxia.

The experiments to investigate these problems were divided into two major groups. The first to investigate actions of the β-adrenoceptor blocking drugs which might indirectly affect coronary flow, and the second to investigate the changes in coronary flow and to relate them to changes in cardiac activity. A preliminary account of some of our findings has been given previously (Chamberlain, Davis & Mason, 1967).

Methods

All the experiments were carried out in dogs. To eliminate effects which might have been due to individual anaesthetic agents, three different anaesthetic procedures were used: (*a*) pentobarbitone sodium B.P. 30 mg/kg injected intraperitoneally or intravenously followed by maintenance doses of 3 to 6 mg/kg intravenously, as required; (*b*) induction with methohexitone sodium 12·5 mg/kg followed by chloralose 50 mg/kg and urethane 500 mg/kg intravenously; (*c*) morphine sulphate 2 mg/kg subcutaneously followed by chloralose 50 mg/kg and urethane 500 mg/kg intravenously after 15 min. In the event, the different procedures for anaesthesia did not affect the results. Artificial respiration was maintained with a Starling pump and air, or air supplemented with oxygen to give a final concentration of at least 40% in the inspired gases.

In the first group of experiments, the chest was opened by a midline incision. The pericardium was opened and stitched to the chest wall to support the heart. Arterial pressure was recorded from a femoral artery using a mercury manometer. Venous pressures were recorded using water manometers connected to cannulae in the jugular vein and left atrium. Heart rate was recorded from the arterial pulse wave using the method of Daly & Schweitzer (1950). In some experiments the arterial pressure or venous pressures were stabilized using large constant pressure reservoirs filled with 3% dextran in normal saline, and connected to the appropriate part of the circulation through a wide bore cannula. The contractions and volume of the heart were recorded using either a Cushny myocardiograph or a glass cardiometer connected to a large tambour. In some of these experiments left intraventricular pressures were recorded through a catheter inserted into the carotid artery, then passed round the aortic arch and through the aortic valves into the

ventricle. The preparations were challenged by intravenous injections of phenylephrine (4–10 μg/kg), noradrenaline (0·2–0·4 μg/kg), adrenaline (0·4–0·8 μg/kg), isoprenaline (0·1–0·2 μg/kg) and by electrical stimulation of the sympathetic fibres leaving either the right or the left stellate ganglion.

In the second series of experiments the anaesthetized animal was laid on the right side and the second, third and fourth ribs on the left side removed. The left lung was removed and the heart supported in a cradle formed from the pericardium. There is evidence that the flow in deep coronary vessels differs from that in vessels nearer the surface, so it was decided to measure total left coronary flow. The coronary circulation in the dog is left dominant (Wolfe, 1959), so this gave a measure of the total blood flow to the left ventricle. The common left coronary is too short to allow the application of a flow transducer (Fig. 1), so we used a modified cannulation technique (Chambliss, Demming, Wells, Cline & Eckstein, 1950; Eckstein, McEachen, Denning & Newberry, 1951). A stainless steel cannula with an internal diameter of 3 mm was inserted through the left subclavian artery, round the aortic arch and into the root of the left coronary artery, where it was tied in place with a ligature round the outside of the artery. Great care had to be taken with the dissection of the artery so that the ligature did not occlude the septal branch, because this rapidly produced cardiac failure and death. At the completion of some of the experiments casts were prepared of the aortic arch and coronary vessels, using acrylic resin injected retrogradely through a cannula in the descending aorta. The casts were used to define the preferred shape of the coronary cannula and to investi-

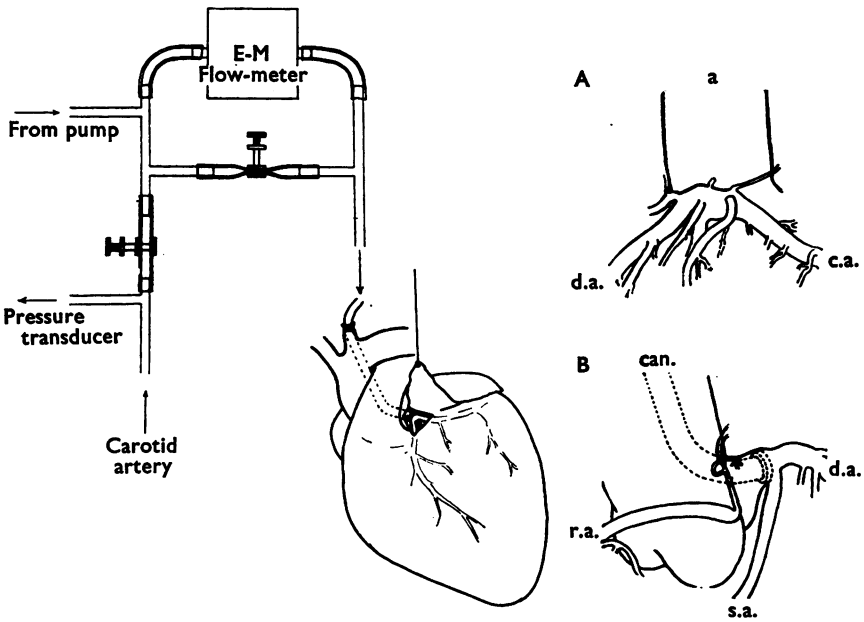

FIG. 1. Diagram to show cannulation of the left common coronary artery through the subclavian artery and the aorta, and the perfusion circuit. Panel A is a drawing from a cast of the coronaries from the angle seen in the dissection. Panel B shows the same cast from the side to show the septal branch and the final position of the cannula. a, Aorta; c.a., circumflex coronary artery; d.a., descending coronary artery; r.a., right coronary artery; s.a., septal branch of left coronary artery; can., outline of perfusion cannula in position.

gate the relations of the major branches of the left coronary artery. The position of the septal branch varied considerably, but in about half the preparations it left the common coronary artery very close to the coronary ostium and crossed the surface of the left aortic valve sinus (Fig. 1). In the remaining preparations this branch arose from the descending coronary artery, adjacent to, or beyond, the separation of the circumflex branch. Blood to supply the coronary circulation was drawn from the left carotid artery and passed through an electromagnetic flow probe to the cannula in the coronary artery.

The electromagnetic flow meter was constructed by our colleague Mr. J. Gasking. It was energized at 400 c/s (sinusoidal) and had a frequency response of 0–15 c/s in the early experiments, and 0–25 c/s in later experiments. A reading for zero flow was obtained at least once every 30 min by diverting the blood flow through a by-pass. These readings were compared with the zero obtained at death and were found to agree. The flow meter was calibrated at the end of each experiment by passing normal saline through at measured rates. The calibration curve was linear and passed through the origin.

Pressures were recorded from the left carotid artery or from the left ventricle, using a catheter inserted through the left atrial appendage and past the mitral valve. It is not possible to examine the frequency response of the pressure transducer and catheter during an experiment, but prior calibration using the method described by McDonald (1960) showed that the system had a frequency response better than the minimum requirements suggested by him. Coronary venous samples were obtained either from a cannula tied into the great coronary vein and connected via a two way tap to the femoral vein, or through a hard polythene catheter inserted through the right atrium and its tip placed in the coronary sinus. Blood pO_2 was measured using a Clark electrode.

The tracings were recorded on a Mingograph 81 ink recorder with a frequency response of 0–700 c/s. The left intraventricular pressures were subsequently analysed for maximum rate of pressure rise during isovolumetric contraction (dp/dt), and for pressure-time index (PTI). In later experiments these parameters were displayed directly using a differentiator with a time constant of 0·001 sec, and an analogue integrator with a time constant of 0·1 sec and a clock period of 5 or 10 sec.

In some experiments heart rate was increased by direct stimulation through electrodes stitched to the right atrial margin. The preparations were challenged: (*a*) by intravenous injections of phenylephrine, noradrenaline, adrenaline, or isoprenaline in similar doses to those used in the first group of experiments; (*b*) by intra-coronary-arterial infusions of isoprenaline; or (*c*) by stimulation of the nerves leaving the left stellate ganglion. The β-adrenoceptor blocking compounds pronethalol (I.C.I. 38,174) or propranolol (I.C.I. 45,520) were infused intravenously over a period of at least ten minutes, except in a few experiments where the responses to rapid injections were examined.

Results

Antagonism to sympathomimetic amines and to sympathetic stimulation

In almost all the experiments the intravenous infusion of pronethalol 1·0 mg/kg or propranolol 0·1 mg/kg prevented the tachycardia due to the intravenous injection

of isoprenaline 0·1–0·2 μg/kg or adrenaline 0·4–0·8 μg/kg, or due to sympathetic stimulation. In a few experiments the blockade was not complete, and adding further doses of the compounds did not increase the blockade. Where blockade was complete, a tachycardia was again produced if the dose of isoprenaline was increased by a factor of two or more. The duration of the blockade was not measured precisely, but in most experiments the tachycardia was beginning to re-appear within 45 min, and in some experiments within 20 min. If the rate of recovery were slightly more rapid in some instances it may account for the occasional failure to produce complete blockade, because infusion of the blocking agents lasted 10 min.

Effects on arterial and venous pressures

In preliminary experiments where the chest was not open, the infusion of β-adrenoceptor blocking doses of pronethalol or propranolol either had no effect on the arterial pressure, or reduced it by 5–15 mm Hg. In experiments in which the chest was opened the compounds reduced the arterial pressure by values up to 40 mm Hg. The depressor response to isoprenaline was also prevented. In twenty-four experiments left atrial pressure was recorded, and in twenty-three experiments

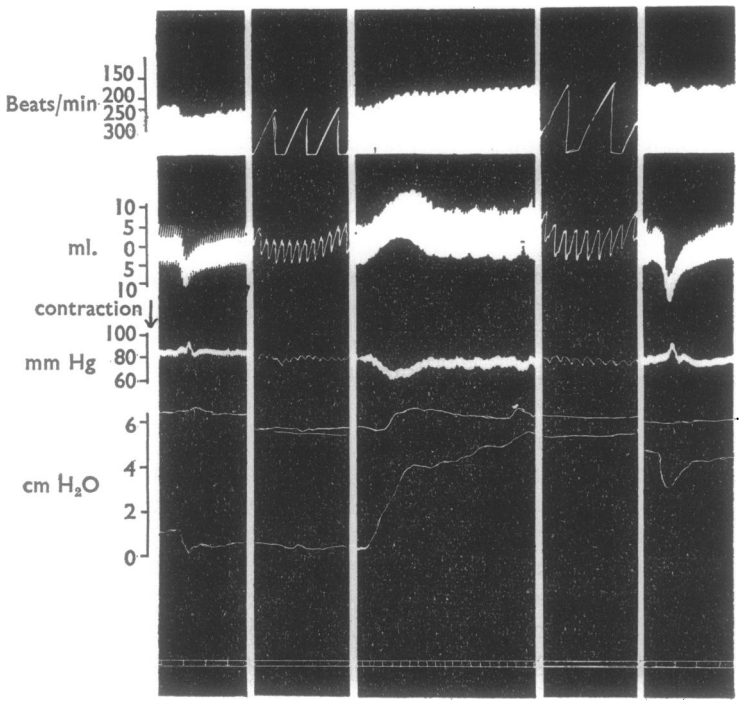

FIG. 2. Dog, 10·8 kg; pentobarbitone anaesthesia; records from top to bottom are heart rate (wider trace—slower rate), ventricular volume measured with a cardiometer, arterial blood pressure which was stabilized, pressure recorded from the right jugular vein, left atrial pressure, time 30 sec. First and last panels show the responses to isoprenaline 10 μg intravenously before and after pronethalol 1 mg/kg (centre panel). Intermediate records on fast drum show ventricular stroke volume between respiratory movements. Pronethalol caused an increase in stroke volume but a decreased heart rate, so that cardiac output was unchanged. Left atrial pressure was raised and the tachycardia due to isoprenaline was inhibited, but not the change in ventricular volume.

central venous (right atrial) pressure was recorded. The infusion of the blocking agents had a variable effect on the venous pressures, but the effects were the same on both sides of the heart and they will be described together. A fall in venous pressure was recorded only once. In one-third of the experiments the venous pressure was unchanged. In the remainder the pressures rose by values up to 60 mm water. Similar changes occurred in the end diastolic pressure in the left ventricle (Figs 2 and 4).

Isoprenaline or sympathetic stimulation reduced left atrial pressure but had little effect on right atrial pressure. This reduction was not always prevented by the β-adrenoceptor blocking compounds. The usual responses to phenylephrine, noradrenaline, and adrenaline were a rise in pressure, which was modified but not prevented by these compounds. Hexamethonium 1·0 mg/kg caused a fall in arterial pressure and a rise in venous pressure.

Effect on heart rate

The heart rate was usually reduced. For example, in the first twelve experiments the mean initial heart rate was 143 beats/min (S.D. 35·9), and the mean rate after pronethalol or propranolol was 103 beats/min (S.D. 10·6). In subsequent experiments with more extensive surgical intervention the initial rate was often higher and the uniformity of the heart rate after the blocking compound was not so apparent, but there was always a reduction in the heart rate.

Effect on heart size

Since none of the available methods for measuring changes in heart size was free from objection, two methods were used and the results compared. In seven experi-

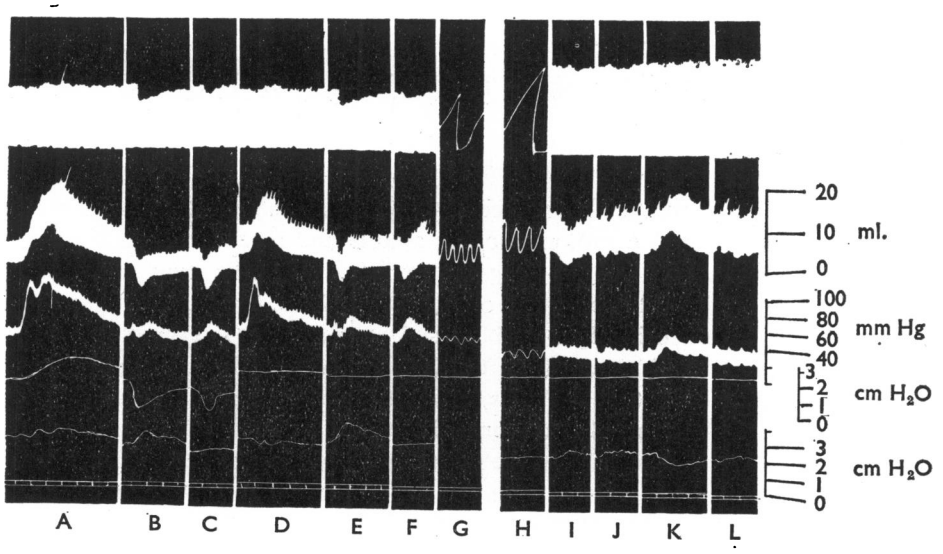

FIG. 3. Dog, 10 kg; pentobarbitone anaesthesia; records as for previous figure, but left atrial pressure above jugular pressure. Responses to phenylephrine 100 μg intravenously in panels A, D, K. Responses to isoprenaline 2 μg intravenously in panels B, E, I, and L. Responses to stimulation of the sympathetic nerves in panels C, F, and J. Left atrial pressure was stabilized between C and D. Propranolol 0·1 mg/kg was infused between fast records G and H, and repeated between K and L.

ments a Cushny myocardiograph was stitched to the left ventricle near, and parallel to, the junction of the left and right ventricles. It was attached to a lever with a light spring to approximate an isotonic system. In ten experiments a cardiometer was applied to the ventricles. The myocardiograph proved difficult to adjust so that it recorded satisfactorily throughout the experiment, but the results agreed with those obtained with the cardiometer. In these experiments application of the cardiometer produced no significant changes in arterial or venous pressures, heart rate, or visible changes in heart action.

When no steps were taken to stabilize either arterial or venous pressures, pronethalol and propranolol caused variable changes in ventricular volume, but most frequently an increase. It was noted that in those experiments where the ventricular volume did not increase, there was a larger than average fall in arterial pressure. Therefore in subsequent experiments the arterial or left atrial pressures were stabilized at or just above their initial values. Under these conditions the infusion of pronethalol or propranolol caused an increase in both the systolic and diastolic volumes of the ventricles. At the same time the stroke volume was increased (Figs 2 and 3). From the records of ventricular volume and heart rate it was possible to calculate approximate values for the cardiac output. Although the measurements were subject to several possible sources of error, the results suggested that the cardiac output was not altered by the infusion of pronethalol or propranolol provided large changes in the arterial pressure were prevented.

Both isoprenaline and sympathetic stimulation caused a considerable decrease in volume, while noradrenaline caused a brief reduction followed by an increase, and phenylephrine caused only an increase. After pronethalol or propranolol the isoprenaline-induced decrease in volume was smaller, but was appreciably more difficult to eliminate than the concurrent tachycardia. The increases in volume due to noradrenaline or phenylephrine were not modified by the blocking drugs, and were probably secondary to the rise in arterial pressure since they were reduced by measures to stabilize the pressure.

Hexamethonium 1 mg/kg produced a reduction in arterial pressure, ventricular volume and stroke volume.

Effect on ventricular pressures

Pronethalol and propranolol produced two changes in the records of the left intraventricular pressures, a prolongation of systole and a reduction in the rate of isovolumetric contraction (dp/dt) (Figs. 4 and 8). The duration of systole is dependent both on the heart rate and on the sympathetic drive. For example, in the experiment illustrated in Fig. 4 and Table 1, stimulating the sympathetic nerves decreased the duration of systole from 0·142 to 0·11 sec. Although the heart rate was increased from 243 to 257 beats/min the proportion of the cardiac cycle represented by systole was reduced from 55 to 47%. When the heart was driven through pacing electrodes applied to the right atrium to increase the heart rate to the same value, systole was shortened from 0·145 to 0·13 sec, but the proportion of the cycle represented by systole was increased slightly from 53 to 56%.

Administration of propranolol 0·1 mg/kg lengthened the duration of systole from 0·144 to 0·191 sec. Since this was accompanied by a reduction in heart rate from 209 to 127, then to 117 beats/min, the proportion of the cardiac cycle represented by systole was reduced from 50 to 40, then to 37%. At this point the heart was

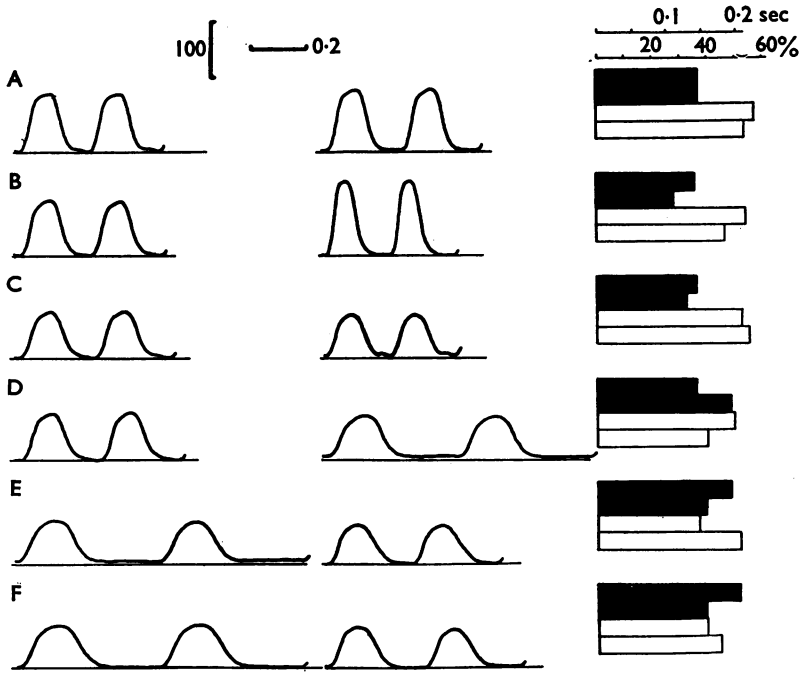

FIG. 4. Dog, 8·9 kg; morphine and chloralose anaesthesia. To the left are tracings of left intraventricular pressures before and after the procedures described below. To the right the duration of systole is shown in seconds (solid blocks) and as a fraction of the cardiac cycle (open blocks). Control observations are uppermost. Records before and after: A, phenylephrine 60 μg intravenously; B, sympathetic stimulation at 10/sec; C, electrical pacing; D, propranolol 0·1 mg/kg; E, electrical pacing; F, aminophylline 70 mg.

TABLE 1. *Effects of sympathetic stimulation and electrical pacing, before and after propranolol* 0·1 *mg/kg and of phenylephrine and aminophylline, in dog* (8·9 *kg*)

Event	Coronary flow (ml./min)	Heart rate (beats/min)	Systolic pressure (mm Hg)	pO_2 (mm Hg) Arterial	pO_2 (mm Hg) Coronary sinus	Duration of systole sec	Duration of systole % of cycle	PTI (mm Hg sec/min)	dp/dt (mm Hg/sec)
Control	47	234	107	138	14	0·147	58	2,820	2,320
Phenylephrine 6·8 μg/kg	49·5	220	115		17	0·147	54	2,870	2,490
Control	36	234	100	118		0·142	55	2,710	2,420
Sympathetic stimulation 10/sec	55	257	135		14	0·11	47	2,790	4,720
Control	28	220	88	110	13	0·145	53	2,240	1,960
Electrical pacing	30	256	82		13	0·13	56	2,170	1,820
Control	28	209	88	113	14	0·144	50	2,140	2,040
Propranolol 0·1 mg/kg	24·5	127	82	135	14	0·191	40	1,610	1,275
After 10 min	21·3	117	80			0·191	37	1,440	1,170
Electrical pacing	25·5	196	75		11	0·157	52	1,915	1,390
(1) Heart did not follow pacing at 236/min. (2) Sympathetic stimulation had no effect.									
Control	16	120	78			0·203	40	1,570	1,115
Aminophylline 7·8 mg/kg	23	175	73			0·154	45	1,650	1,375

driven electrically at a rate of 196 beats/min. The duration of systole was reduced from 0·191 to 0·157 sec, representing 52% of the cardiac cycle, an increase. The ventricles would not follow rates of stimulation greater than this, so that it was not possible to match accurately the heart rate before blockade of the β-receptors. The responses to sympathetic stimulation were inhibited.

Infusion of isoprenaline into the left coronary artery of normal preparations reduced both the duration of systole and the proportion it represented of the cardiac cycle (0·178–0·124 sec: 38–28%), but only when the compound was infused at rates of the order of 0·96 μg/min.

The maximum rate of pressure rise during isovolumetric contraction of the ventricle (dp/dt) has been suggested as a measure of the contractility of the myocardium. The effect on dp/dt was measured in seventeen experiments. Following β-adrenoceptor blockade, it declined in every experiment, over a range of 15 to 73% (mean 40%).

When expressed as dp/dt, the contractility of the heart is found to be modified by several factors including the sympathetic drive to the heart, the heart rate, and the mean arterial pressure. Table 1 shows the results from one of the experiments to compare the influence of two of these factors. In the normal heart with an intact sympathetic innervation, electrical stimulation of the sympathetic nerves increased dp/dt from 2,420 to 4,720 mm Hg/sec, an increase of 95%. When the heart was driven electrically to give a similar increase in heart rate, dp/dt declined slightly from 1,960 to 1,820 mm Hg/sec, a decrease of 7%. Infusion of propranolol 0·1 mg/kg reduced dp/dt from 2,040 to 1,275 mm Hg/sec, a decrease of 37%. Pacing the heart at a rate near to that before propranolol raised dp/dt from 1,170 to 1,390 mm Hg/sec, an increase of 19% on the unpaced value, but still 31% less than the value before propranolol.

These experiments suggested that the alteration in the sympathetic drive and not the change in heart rate was the more important factor. This is in agreement with the observation that in the normal heart, infusion of isoprenaline into the left coronary artery at a rate of 0·96 μg/min increased dp/dt from 2,710 to 7,240 mm Hg/sec, an increase of 168%, although the heart rate was only increased from 124 to 138 beats/min by the isoprenaline carried round the circulation to the left coronary and the pacemaker.

Control of the arterial pressure did not prevent the reduction of dp/dt after blockade of the β-adrenoceptors.

Effect on pressure-time index

The pressure-time index (PTI) has been proposed as a measure of the work done by the heart. In seventeen experiments this was calculated by measuring the mean ventricular pressure during systole and multiplying by the duration of systole and the heart rate. As has been shown already, the duration of systole was increased and the heart rate decreased after β-blockade. These changes had opposite effects on the PTI, but the change in heart rate was proportionally greater than the change in duration of systole and, coupled with some reduction in the mean systolic pressure, resulted in a decrease in PTI in all except one experiment, where there was no change. The mean reduction of PTI was 30%, with a range of 0 to 57%.

In a further nine experiments where only slow records of the arterial pressure were

available, an indication of PTI was obtained by the method of Parratt & Grayson (1966) using the product of the systolic pressure and the heart rate. This value was also reduced (range 11 to 41%) by β-blockade, but since the calculation takes no account of the changes in the duration of systole it only serves as an indication.

In normal preparations, stimulation of the left sympathetic nerves always resulted in a reduction of the PTI both when heart rate was increased and when it was not altered and although peak systolic pressure was raised. This reduction in PTI was produced by the considerable shortening of systole.

Effects on coronary flow

Total left coronary flow was measured in twenty-six experiments. The records displayed both mean and phasic flow, so that a measure of relative changes in systolic and diastolic flow could also be obtained. Although care was taken to keep the system as compact and as rigid as possible, the need to allow for the movements of the heart necessitated some flexible connections between the flow head and the steel cannula. The attendant small degree of elasticity may have slightly damped the higher frequency changes in flow. The blood for the system was drawn from the left carotid artery, so that there was some phase change between the contraction of the ventricles and the appearance of peak systolic pressure in the perfusion system, when compared with the natural circulation. Despite these factors, the observed flow patterns were in general agreement with those observed by previous workers, including those made with cuff flowheads applied to branches of the coronary artery. Peak flow occurred during diastole. During systole the average flow was often as little as half the diastolic flow. In some experiments there was a brief period during systole when flow almost stopped, but we have never recorded reverse flow, as has been seen by some workers. This pattern of peak

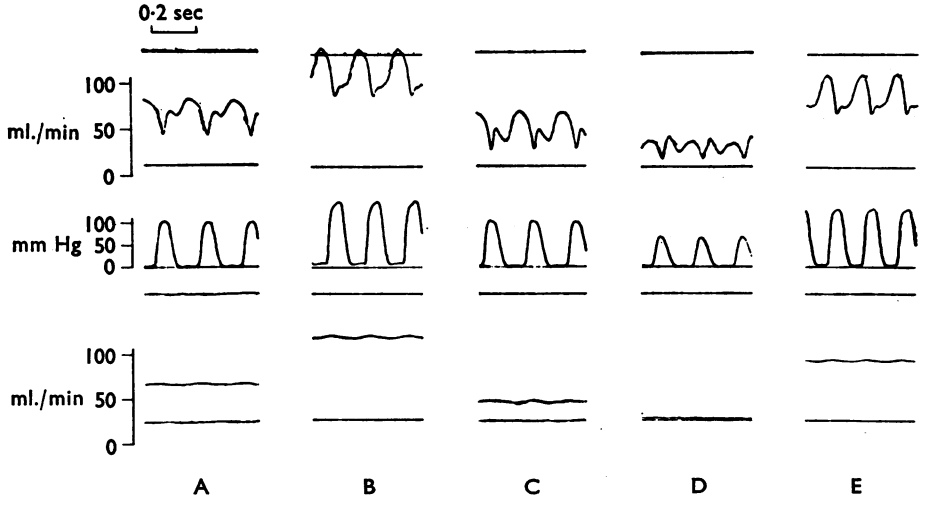

FIG. 5. Dog, 9 kg, methohexitone induction, chloralose-urethane anaesthesia. Records from the top, Phasic coronary flow, left intraventricular pressure, mean coronary flow. A, control; B, after infusion of dextran; C and D, stages in a stepwise haemorrhage; E, after re-infusion of blood.

diastolic flow and reduced systolic flow persisted throughout the normal range of blood pressures. In some preparations in which the arterial pressure was reduced to very low values, the flow during systole became more important and even predominated (Fig. 5).

Maximal stimulation of the sympathetic nerves at frequencies of 5–20/sec produced increases of 20 to 100% in flow which were concurrent with changes in heart rate, dp/dt and PTI which have already been described. Juhász-Nagy & Szentiványi (1961) and Szentiványi & Juhász-Nagy (1963) found that sub-maximal stimulation at a low rate could cause a reduction in coronary flow. In the present experiments a stimulation rate of 5/sec with a pulse width of 0·1 msec no longer produced any increase in heart rate or dp/dt, but a small reduction in flow (10–15%) and in PTI occurred. Attempts to obtain similar effects by reducing the strength of the stimuli instead of the pulse width were without success.

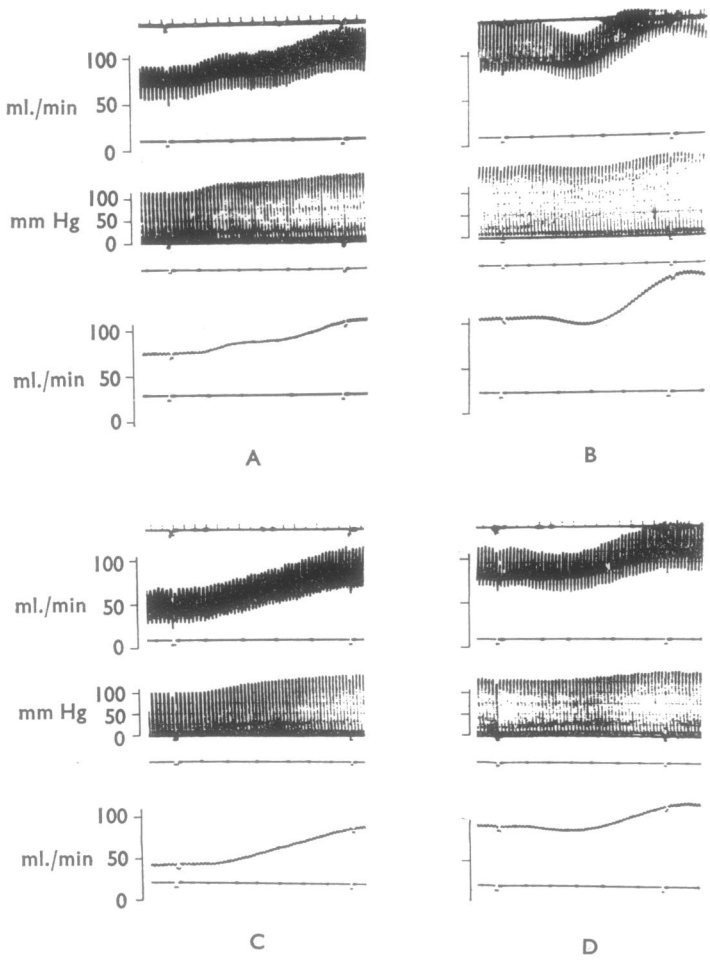

FIG. 6. This is the same experiment as Fig. 5, and shows the response to stimulation of the sympathetic nerves at corresponding stages in the experiment: Panel A, control record, corresponding to panel A in Fig. 5; Panel B, after dextran infusion, corresponding to panel B in Fig. 5; Panel C, during haemorrhage, corresponding to panels C-D in Fig. 5; Panel D, during the re-infusion, corresponding to panels D-E in Fig. 5.

In some, but not all, preparations with a high arterial pressure, maximal stimulation of the sympathetic nerves caused a brief reduction in flow before the increase already described. In an experiment where this response was elicited, the influence of arterial pressure on this response was investigated (Fig. 6). The animal was first infused with a volume of dextran equal to 25% of its calculated blood volume. The response to sympathetic stimulation was recorded, then 50 ml. of blood was withdrawn from a major artery. Stimulation followed by haemorrhage was repeated until the arterial pressure reached a very low level. The blood was then re-infused in 50 ml. volumes, the infusions interspersed with periods of sympathetic stimulation. It was found that when the arterial pressure and coronary flow were high, stimulation of the sympathetic nerves caused a brief vasoconstriction followed by vasodilatation. When the pressure was lowered the flow was less and now stimulation only produced a vasodilatation. When the blood was re-infused and the pressure and flow raised, the brief preliminary vasoconstriction re-appeared (Fig. 6).

The intravenous injection of adrenaline, noradrenaline or isoprenaline also produced an increase in flow, but in our experiments this was never preceded by a vasoconstriction. The intra-arterial (coronary) injection of phenylephrine in doses of 2 or 4 μg caused a small vasoconstriction without any change in peak systolic pressure, dp/dt, or PTI. Increasing the dose up to 32 μg phenylephrine did not increase the vasoconstriction, which never exceeded 15% of the flow. Procedures which increased the coronary flow, such as reducing the oxygen tension of the blood, or infusing dextran, did not increase the vasoconstrictor response. The intravenous injection of phentolamine 0·35 mg/kg almost eliminated the response. The intra-arterial injection of noradrenaline in doses of 0·2 to 0·8 μg caused only a small increase in flow accompanied by an increase in dp/dt and a reduction in PTI.

Intra-arterial (coronary) infusions of isoprenaline at a rate of 0·6 or 0·92 μg/min produced an increase in dp/dt and a reduction in PTI, as a result of shortening of systole, but coronary flow was unchanged. Increasing the rate of infusion to 2·4 μg/min produced greater changes in dp/dt and PTI, but now the coronary flow was increased by 200% and more.

The intravenous infusion of pronethalol (1·0 mg/kg) or propranolol (0·1 mg/kg) either had no effect, or, more usually, produced a reduction in coronary flow (Figs. 7, 8 and 9). In twenty-six experiments the mean effect was a reduction of 32% (range 0 to 86%). An increase in flow was never recorded. The flow pattern remained substantially the same, with diastolic flow greater than systolic flow except where the perfusion pressure fell considerably, when systolic flow assumed a greater importance. Although there was often a reduction in arterial pressure at the same time as the reduction in flow, this was not great enough to account wholly for the change in flow. Thus in seven experiments where arterial pressure was routinely recorded instead of intra-ventricular pressure, the blockade of the β-adrenoceptors caused a reduction in the flow of 26%, while mean arterial pressure only fell by 10%, indicating that there was an increase in coronary resistance. Similarly in an experiment where the mean arterial pressure was stabilized, propranolol 0·1 mg/kg still caused a reduction in flow, indicating that there was an overall increase in coronary resistance.

After β-blockade, stimulation of the sympathetic nerves was without effect on the flow. The intravenous injection of isoprenaline was also without effect. When other sympathomimetics were administered there was no effect on flow, except when

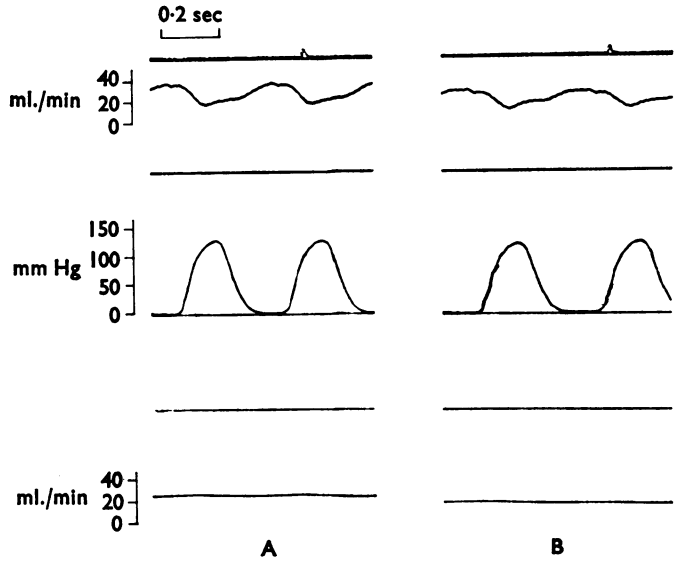

FIG. 7. Dog, 11 kg, methohexitone induction, chloralose-urethane anaesthesia. Records from the top: phasic left coronary flow; left intra-ventricular pressure; mean coronary flow. Records before (A) and after (B) the slow infusion of pronethalol 1 mg/kg.

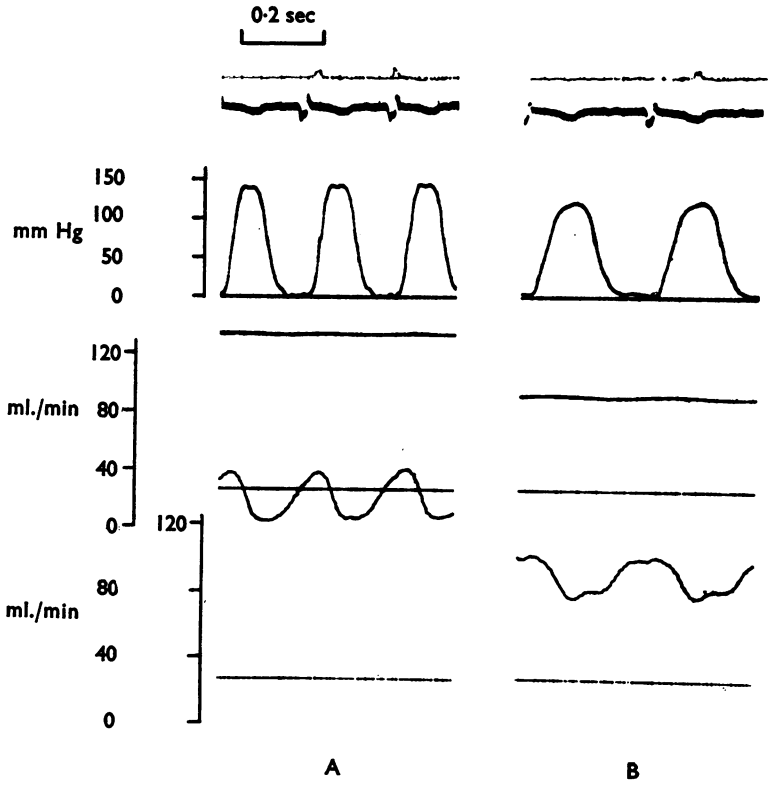

FIG. 8. Dog, 11 kg, methohexitone induction, chloralose-urethane anaesthesia. Records from the top: e.c.g., left intra-ventricular pressure, mean coronary flow, phasic coronary flow. Records before (A) and after (B) the slow infusion of propranolol 0·1 mg/kg.

the compound produced a rise in pressure (for example, phenylephrine), whereupon flow was also increased. Administration of phentolamine (0·4 mg/kg) after the β-adrenoceptor blockade produced a reduction in arterial pressure and in coronary flow. These changes were similar fractions of the control values, and were similar in time of onset. After β-adrenoceptor blockade, reduction in the oxygen content of the respired gases, or reduction in the stroke volume of the artificial respiration, still produced an increase in flow.

Increasing the heart rate by electrical pacing of the right atrium caused an increase in coronary flow, but this was small compared with the increase caused by stimulation of the sympathetic nerves, although the increase in heart rate was similar in both cases. Thus in a normal animal, stimulation of the sympathetic nerves increased the heart rate from 234 to 257 beats/min, and increased coronary flow from 36 to 54 ml./min. Increasing the heart rate from 220 to 257 beats/min by pacing stimuli increased coronary flow from 28 to 30 ml./min. Following propranolol 0·1 mg/kg the heart rate fell to 117 beats/min and the flow from 28 to 21·3 ml./min. After the blockade, pacing the heart at 196 beats per min increased the flow to 25·5 ml./min, which was 91% of the value before β-adrenoceptor blockade. This dose of propranolol had reduced the PTI from 2,140 to 1,440 mm Hg/sec, while pacing the heart increased the PTI to 1,915 mm Hg/sec, which is 89% of the control value. dp/dt was increased by pacing, but only from 57% to 67% of the control value.

Effect on arterial and coronary venous oxygen tensions (pO_2)

In this series of experiments, the open chest preparations were ventilated with air supplemented with oxygen to give a final concentration of approximately 40%. With this mixture the arterial pO_2 was initially higher, and usually remained higher, than the arterial pO_2 found in the anaesthetized preparations breathing air spontaneously, before the thorax was opened. During the experiment the arterial pO_2 declined slowly, and further increases in the concentration of oxygen in the inspired gases did little to prevent this. Values for the arterial pO_2 before the chest was

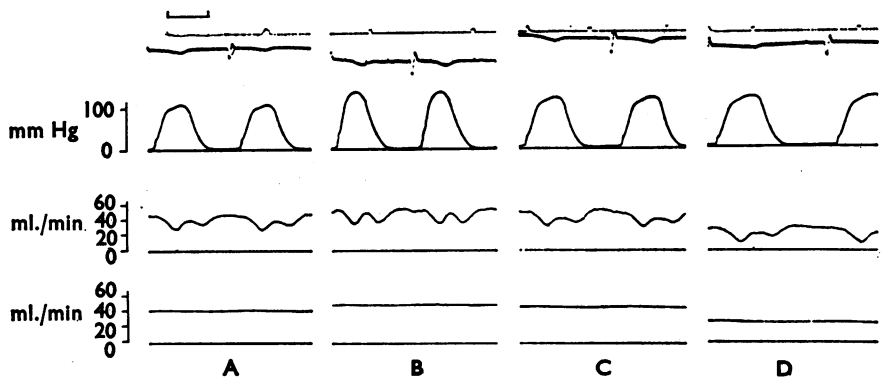

FIG. 9. Dog, 11 kg, pentobarbitone anaesthesia. Records from the top: e.c.g. left intraventricular pressure, phasic coronary flow, mean coronary flow. Records taken before (A) and during (B) stimulation of the sympathetic nerves, then before (C) and after (D) propranolol 0·1 mg/kg.

opened, or artificial respiration instituted, ranged from 70 to 100 mm Hg. After commencing artificial respiration the pO_2 increased to 130–150 mm Hg. By the time the dissection, setting up, and a control period were complete, the pO_2 had declined. In a few experiments the value fell to 60 mm Hg, but in most it remained between 110 and 140 mm Hg. The fall was presumably due to progressive changes in the lung. There was no evidence of pulmonary oedema, and a spontaneous atelectasis may have been the cause. As reported by previous workers the coronary venous pO_2 was much lower than the mixed venous pO_2, suggesting that oxygen extraction was more complete. The mean control value for coronary venous pO_2 was 25 mm Hg, with most of the values between 14 and 33 mm Hg. In a single experiment the value was 62 mm Hg. Although the coronary venous oxygen tension varied between experiments, within each experiment the values remained almost constant and did not reflect the decline in arterial pO_2. Procedures which caused large changes in coronary flow (sympathetic stimulation, injection of isoprenaline) caused either no change in coronary venous oxygen tension, or changes which were only just larger than experimental error. Where changes occurred, sympathetic stimulation or isoprenaline reduced venous pO_2, thus slightly increasing arterial–venous oxygen difference, suggesting an increased oxygen extraction.

The effect of pronethalol and propranolol on arterial and coronary venous oxygen tension was examined in fourteen experiments. The arterial pO_2 declined slightly or remained constant in eleven experiments. This decline was always small and was no greater than the slow decline observed in the control period already described. In three of the experiments the arterial oxygen tension increased.

In the thirteen experiments where the control venous pO_2 was between 14 and 33 mm Hg, the addition of the β-adrenoceptor blocking drugs caused small changes in either direction, but a mean reduction in pO_2 of 4 mm Hg. In the single experiment with an elevated control pO_2, propranolol caused a larger reduction in venous pO_2 (35 mm Hg), giving a mean for the whole group of 6 mm Hg. It is worth noting that the reduction in the venous pO_2 was 4 mm Hg or less in nine of the fourteen experiments, and was reminiscent of the constancy of the values obtained in the control period.

Discussion

A reduction in coronary flow, such as that seen after pronethalol or propranolol, may be the result of changes in the tone of the coronary vessels, or of changes in factors which exert an indirect influence on the flow. The first factor to be considered was the effective perfusion pressure. In the present experiments the reduction in the total left coronary flow was usually greater than the reduction in the arterial pressure, and in two experiments where the arterial pressure was unchanged the coronary flow was reduced by 21 and 29%. Venous pressure was usually raised by pronethalol and propranolol, but the rise in venous pressure or of left ventricular end diastolic pressure did not bear any consistent relationship to the reduction in coronary flow. This apparent independence of coronary flow and effective perfusion pressure within the limits of these experiments is similar to the variable relationship of flow and arterial pressure or flow and venous pressure reported by Gregg in experiments where the two pressures were modified but sympathetic drive was not varied (Gregg, 1950; Driscol, Moir & Eckstein, 1964).

Diastole represented the period of maximum flow, but changes in the relative durations of systole and diastole were not related to changes in flow. It was possible to induce changes in the duration of parts of the cardiac cycle while coronary flow changed in either a similar or in an opposite direction. Thus, stimulation of the sympathetic nerves to the heart reduced the proportion of the cardiac cycle occupied by systole and increased the proportion occupied by diastole. This change was accompanied by an increased flow. Administration of a β-adrenoceptor blocking drug also increased the proportion of the cardiac cycle occupied by diastole, but the mean coronary flow was reduced.

The flow during systole was usually smaller than during diastole but still represented a significant fraction of the total flow. If, following β-adrenoceptor blockade, the extra-mural pressure on the vessels was increased so that the flow during systole was reduced or even prevented, this might account for some reduction in the mean flow. The extra-mural pressure is related to the wall tension in the ventricle, which is in turn related to the intraventricular pressure and to the mean diameter of the ventricle (Taylor, Cingolani, Graham & Clancy, 1967). In our experiments intraventricular pressures were either unchanged or reduced by β-adrenoceptor blockade, which would tend to reduce wall tension. The records with cardiometer and myocardiograph confirmed the visual observation that the heart size was increased after β-adrenoceptor blockade. This agreed with the observations of Donald, Kvale & Shepherd (1964) and those in man by Chamberlain & Howard (1964), and would mean an increase in the wall tension developed during systole for the same intraventricular pressure. Since the ventricle is not a simple shape, and since the increase in ventricular volume was partly due to an increase in length, it was not possible to calculate the change in wall tension, and hence the change in extra-mural support. The records of phasic flow, however, showed that the flow during systole was not more reduced than the flow during diastole by pronethalol or propranolol. Further, it is worth noting that even complete cessation of the flow during systole would not have accounted for the reduction in mean flow recorded in some of the experiments. In those experiments where the systolic pressures were greatly reduced by β-adrenoceptor blockade, the flow during systole increased and even exceeded the diastolic flow, giving a flow pattern similar to that seen after acute reduction of the circulating volume.

Since none of the changes in the extra-coronary factors seem adequate to explain the observed reduction in coronary flow after pronethalol or propranolol the change must be due to a direct change in coronary resistance or tone. Coronary flow is greatly altered by the changes in the level of sympathetic nervous activity, but in the normally beating heart this is usually accompanied by changes in the activity of the heart, so that it is not clear which is cause and effect or whether they are coincidental. Changes in the external work of the heart, brought about by other means, however, are accompanied by changes in coronary flow also. Changes in pressure work done by the heart produce greater changes in coronary flow and oxygen consumption than changes in cardiac output without a change in pressure (Katz & Feinberg, 1958). In the present experiments the pressure work done by the heart was measured as the pressure–time index. This was reduced by β-adrenoceptor blockade, as was dp/dt, which is sometimes suggested as a measure of contractility (Benfey, Greef & Heeg, 1967). When the reduction in PTI was expressed as a percentage of the control value it was found to be similar to the reduction in

coronary flow, similarly expressed, in most of the experiments, but over all there was not a close enough relationship to justify suggesting a causal relationship. Such a relationship may be involved (Monroe & French, 1961), but some evidence suggests that the sympathetic nerves can cause a direct vasodilatation in addition to the work or metabolically controlled dilatation (Brown, 1968; Klocke, Kaiser, Ross & Braunwald, 1964, 1965). In the majority of experiments the arterial/coronary venous pO_2 difference was little changed by propranolol or pronethalol, suggesting that measurements of coronary flow provided some indication of changes in myocardial oxygen consumption. Observations in man also show that the coronary sinus oxygen saturation was not reduced (Mendel & Byrne-Quin, 1966). Since the coronary venous pO_2 was usually so low, any reductions produced by β-adrenoceptor blockade were necessarily small and it is difficult to adduce support for or against suggestions that the reductions in cardiac work may have been the result of an inadequate supply of oxygen, except in the few experiments where the pO_2 was unusually high. Here, β-blockade produced some reduction in the coronary venous pO_2 but not to values as low as those obtained in the control period of other experiments. The significance of the rise in arterial pO_2 seen in three experiments is not clear.

The clinical reports that patients with angina pectoris who are receiving β-adrenoceptor blocking drugs can exercise more vigorously before there is evidence of myocardial anoxia in the e.c.g. (MacAlpin, Kattey & Winfield, 1965) would suggest that oxygen lack is not the factor which reduces myocardial work. Parratt & Grayson (1966), however, suggested that these compounds abolished vasodilator tone and unmasked a vasoconstrictor action mediated through α-adrenoceptors. In our experiments, stimulation of the sympathetic nerves after β-adrenoceptor blockade never produced a vasoconstriction, although in the control period the effects were the same as those seen by previous workers, that is, a vasoconstriction followed by a dilatation (Berne, de Geest & Levy, 1965; Brachfeld, Monroe & Gorlin, 1960; Granata, Olsson, Huvos & Gregg, 1965; Juhász-Nagy & Szentiványi, 1961). Intravenous injections of adrenaline, noradrenaline or phenylephrine did not reduce coronary flow after β-adrenoceptor blockade. This was similar to the results obtained by Parratt (1965) and Gaal, Kattus, Kolin & Ross (1966), although Parratt calculated that coronary resistance had been increased, and Gaal *et al.* obtained a reduction in flow when noradrenaline was injected intra-arterially. It is worth noting that in all the normal experiments where it was recorded continuously there was a reduction in PTI at the same time as the reduction in coronary flow and before the usual increase in flow. If blockade of the β-adrenoceptor resulted in a preparation with an increased coronary resistance mediated by the α-receptors, then the administration of an α-blocking agent should produce a dilatation of the coronary vessels. In our experiments, phentolamine failed to produce any increase in flow but rather a decrease. This decrease was accompanied by a fall in arterial pressure which might have accounted for the reduction in flow, either because of the reduced perfusion pressure, or because of the reduced PTI, or cardiac work. Olivares, Smith & Aronow (1967) demonstrated that there was an interaction between α- and β-adrenoceptor blocking agents, but this could not account for the reduction in flow observed.

The administration of β-blocking drugs did not render the coronary vessels unresponsive and unable to respond to meet the metabolic demands. Guz, Kurland & Freedberg (1960) have demonstrated a relationship between coronary flow and

oxygen supply. In our experiments, reduction of the oxygen content in the inspired gases resulted in a coronary dilatation after β-blockade as well as before, and similar to that seen in cats by Brown (1968). Reduction of the artificial ventilation, so that carbon dioxide accumulated, in addition to the reduced oxygen content, caused an even greater dilatation. The disappearance of the constrictor responses when the blood pressure, and hence the perfusion pressure, was reduced by haemorrhage suggests that this failure to record vasoconstriction after β-blockade was not a direct effect of the drug concerned, but might be due to a physiological mechanism to limit or prevent excessive vasoconstriction.

All the experimental observations are consistent with the suggestion that the effects produced by pronethalol and propranolol are entirely due to blockade of β-adrenoceptors and not due to a direct effect on the myocardium (Mendel, 1966; Redding & Russel Rees, 1966; Flacke, Osgood & Bendixen, 1967).

Our results lend support to the suggestion that in these experimental conditions there are three mechanisms which affect the coronary circulation. There is a sympathetically mediated constrictor response which is small and not easily elicited alone. There is a sympathetically mediated vasodilator response, which is always accompanied by an increased cardiac activity and which can over-ride the constrictor response. Then there is an autoregulatory control (Driscol *et al.*, 1964) which limits or prevents the constrictor response when flow is reduced. It is conceivable that the sympathetically mediated vasodilatation is an outcome of the autoregulatory control and derives from a primary increase in cardiac activity. The present experiments provide no evidence on this point.

Two of the preparations which received pronethalol died almost immediately. None of the preparations which received propranolol alone died as a direct result. When phentolamine was administered after the β-adrenoceptor blocking drug, only those preparations with a good blood pressure survived. The others died rapidly due to a fall of the blood pressure to below 30 mm Hg, followed by ventricular fibrillation. The extreme fall in pressure was accompanied by an equally large reduction in coronary flow, and was probably the cause of the fibrillation.

The experimental results reported here are in accord with the view that the reduction in coronary flow following β-adrenoceptor blockade is a consequence of, or is associated with, a reduction in cardiac work and hence oxygen demand. An autoregulatory mechanism prevents any excessive sympathetically mediated vasoconstriction.

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