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THE EFFECT OF PROSTAGLANDIN E_1 UPON THE GENERAL AND CORONARY HAEMODYNAMICS AND METABOLISM OF THE INTACT DOG

BY

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The prostaglandins are unsaturated hydroxy-carboxylic acids, which for many years have been known to have vasodepressor and smooth-muscle stimulant properties (von Euler, 1937); one of these, prostaglandin E_1 (PGE_1), has been synthesized (Bergström, Ryhage, Samuelsson & Sjövall, 1962); the natural PGE_1 has been shown to reduce blood pressure and increase heart rate in man and animals (Bergström, Carlson, Ekelund & Orö, 1965; Bergström, Carlson & Orö, 1966). There is, however, no integrated study of the effect of this substance on general and cardiac haemodynamics and metabolism; accordingly, such a study was made, and the results are now presented.

METHODS

Ten apparently healthy dogs weighing from 13–17 kg were given morphine sulphate (3 mg/kg, subcutaneously). After 1 hr, a mixture of pentobarbitone (12.5 mg/kg), allobarbitone (12.5 mg/kg), monoethylthiourea (50 mg/kg) and urethane (50 mg/kg) was injected intravenously. A cuffed tube was placed in the trachea.

The external jugular veins were isolated and standard cardiac catheters placed therein; under fluoroscopic control one catheter tip was placed in a main branch of the pulmonary artery and another in the coronary sinus. The position of the latter was verified by its characteristic *x*-ray silhouette, and by aspiration through it of blood which was much reduced in oxygen content compared to a sample from the pulmonary artery. A Cournand needle was inserted percutaneously into each femoral artery. Catheters and needles were connected to a manifold system which allowed pressures to be measured and blood samples taken.

One hour after administration of the intravenous anaesthetic, cardiac output was calculated by the Fick principle from measurements of gas exchange and blood gas concentrations. Expired air was collected from the endotracheal tube into a Tissot spirometer, whence the minute volume was determined. The gas was collected for 5 min and appropriate blood samples were taken at the midpoint of the collection.

Immediately after the determination of cardiac output, coronary flow was measured by the nitrous oxide saturation method. During this period the animal breathed a gas mixture containing nitrous oxide (15%), oxygen (21%) and nitrogen (64%). Mean coronary flow was estimated over a 10 min period.

Pressures were measured in the pulmonary artery and femoral artery twice during the cardiac output and coronary flow determinations; mean pressures were electrically derived from the strain gauge outputs, and recorded on a direct-writing instrument. Expired air samples were analysed for oxygen and carbon dioxide in a Scholander apparatus. Blood samples were analysed for nitrous oxide, oxygen, and carbon dioxide in a manometric Van Slyke apparatus. Blood sugar was measured by the glucose-oxidase method (Huggett & Nixon, 1957), lactate and pyruvate enzymatically (Horn & Bruns, 1956), and non-esterified fatty acid (NEFA) by the method of Trout, Estes & Friedberg (1960). Insulin-like activity was measured by a modification of the method of Morgan & Lazarow (1963). After 30 min from the control measurements, the effect of prostaglandin E_1 was examined. The drug (0.4–0.5 mg) was appropriately dissolved (Pike, 1967) to a volume of 25 ml. Sufficient solution was injected into a catheter in the inferior vena cava to lower the systemic pressure to at least 75% of its control value. The systemic pressure was constantly monitored, and a steady state of hypotension maintained by the intermittent infusion of the PGE_1 solution during the second measurement of cardiac output and coronary flow; the average dose was found to be 1.5 μg/kg/min. Preliminary studies showed that the solvent had no effect on the systemic pressure or heart rate of 3 dogs. The solution was freshly prepared for each study, and kept cold until used. The volume of infusate never exceeded 25 ml. The animal then always acted as its own control for each of the variables measured. The reproducibility of the general methods has been previously reported (Maxwell, Castillo, Crumpton, Clifford & Rowe, 1959; Maxwell, 1966).

RESULTS

These are presented as group means with standard deviations; statistical analysis was carried out using Student's *t* test, and statistical significance was accepted at the 5% level.

The immediate effects of the infusion of PGE_1 are shown in Fig. 1; the increase in mean pulmonary artery pressure was transient, seldom lasting for more than 1 min; the tachycardia and systemic hypotension persisted.

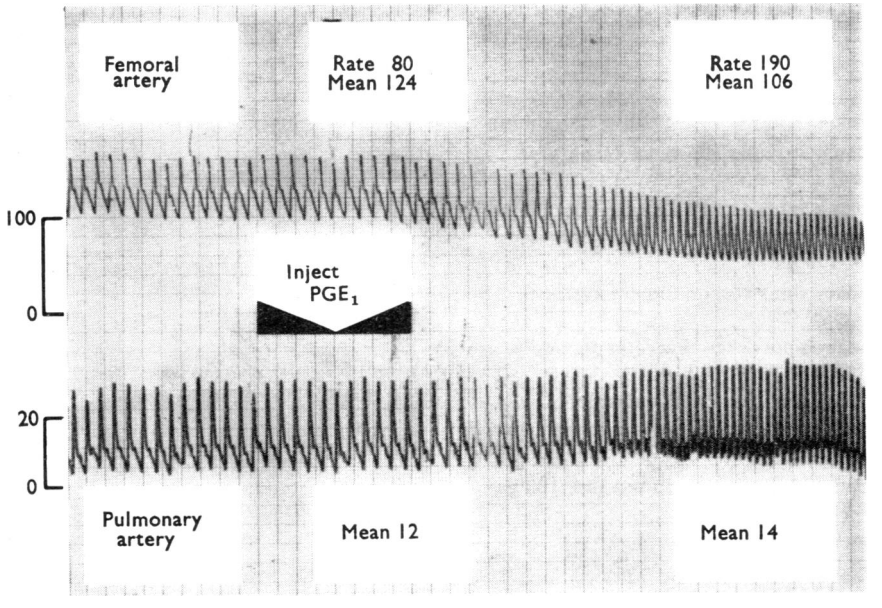

Fig. 1. Immediate effects of prostaglandin E_1 on heart rate and vascular pressures (scale mm Hg).

TABLE 1

THE EFFECT OF INTRAVENOUS INJECTIONS OF PROSTAGLANDIN E_1 ON THE METABOLISM AND HAEMODYNAMICS OF ANAESTHETIZED DOGS

Factor	Control	During Infusion of PGE_1	P
Minute volume (l./min)	2·3±0·38	2·98±0·73	<0·01
Respiratory rate (breaths/min)	13±4	15±6	<0·05
Oxygen consumption (ml./min)	85±12	102±22	<0·01
Carbon dioxide production (ml./min)	66±13	78±24	<0·02
Arterial—mixed venous oxygen difference (ml./100 ml.)	4·3±0·6	3·8±0·8	<0·05
Mixed venous—arterial carbon dioxide difference (ml./100 ml.)	3·7±1·5	2·9±1·2	<0·2>0·1
Cardiac output (l./min)	1·98±0·35	2·68±0·75	<0·01
Heart rate (beats/min)	78±12	165±21	<0·001
Femoral arterial pressure (mean mm Hg)	127±19	101±10	<0·01
Pulmonary arterial pressure (mean mm Hg)	12·9±2·2	13·4±3·8	<0·6>0·5
Left ventricular work (kg/M/min)	3·42±0·94	3·69±1·1	<0·2>0·1
Right ventricular work (kg/M/min)	0·35±0·07	0·49±0·18	<0·01
Total peripheral resistance (c.g.s. units)	5126±907	3012±776	<0·001
Total pulmonary resistance (c.g.s. units)	521±136	400±116	<0·01

Values are means with standard deviation.
Gas volumes are S.P.T.D.

TABLE 2

THE EFFECT OF INTRAVENOUS INJECTIONS OF PGE_1 ON THE MYOCARDIAL CIRCULATION AND OXYGEN AND CARBON DIOXIDE EXCHANGE

Factor	Control	During Infusion of PGE_1	P
Coronary blood flow (ml./100 g heart/min)	80±8	112±24	<0·01
Coronary vascular resistance (arbitrary units)	1·59±0·28	0·90±0·26	<0·001
Coronary sinus oxygen content (ml./100 ml.)	5·4±1·1	4·4±1·6	<0·05
Arterial—coronary sinus oxygen difference (ml./100 ml.)	12·1±1·4	13·8±1·3	<0·02
Coronary sinus carbon dioxide content (ml./100 ml.)	56·9±3·9	54·9±3·7	<0·05
Coronary sinus-arterial carbon dioxide difference (ml./100 ml.)	9·0±1·8	10·7±1·6	<0·05
Cardiac respiratory exchange ratio	0·74±0·08	0·77±0·07	<0·8>0·7
Cardiac oxygen consumption (ml./100 g heart/min.)	9·7±1·1	15·4±3·1	<0·001
Cardiac carbon dioxide output (ml./100 g heart/min)	7·2±1·3	11·9±2·1	<0·01
"Index of efficiency"	0·35±0·09	0·24±0·08	<0·01

Values are means with standard deviation.
Gas volumes are S.P.T.D.
The "index of efficiency" is the ratio of left ventricular work to the cardiac oxygen consumption.

Table 1 shows the results for general haemodynamics and metabolism. In addition to the values given, haemoglobin concentration increased (14.2 to 14.8 g/100 ml.), as did arterial oxygen content (17.8 to 18.3 ml./100 ml.); saturation did not change (91.5 to 91.7%). The mixed venous oxygen content increased significantly (13.4 to 14.5 ml./100 ml.); there was a decrease in the carbon dioxide contents of arterial and mixed venous blood samples (51.0 to 48.9; 47.3 to 46.0 ml./100 ml. respectively). It is clear that stroke volume decreased (27 to 18 ml./beat). Whole-body respiratory quotient was unchanged (0.78 to 0.75); the other results are shown in Tables 2 and 3 respectively.

TABLE 3

THE EFFECT OF INTRAVENOUS INJECTIONS OF PROSTAGLANDIN E_1 UPON SEVERAL BIOCHEMICAL PARAMETERS

Factor	Control	During Infusion of PGE_1	*P*
Glucose-artery (mg %)	101±19	88±15	<0·05
Glucose coronary sinus (mg %)	99±12	88±9	<0·05
Lactate—artery (mg %)	7·33±2·59	8·56±2·5	<0·2>0·1
Lactate—coronary sinus (mg %)	4·57±2·28	5·37±2·64	<0·05
Pyruvate—artery (mg %)	0·81±0·42	0·47±0·21	<0·02
Pyruvate—coronary sinus (mg %)	0·81±0·23	0·80±0·39	<0·9>0·8
Non-esterified fatty acid-artery (m-equiv/l.)	0·58±0·25	0·44±0·22	<0·02
Non-esterified fatty acid—coronary sinus (m-equiv/l.)	0·33 ±0·15	0·27±0·17	<0·05

Figures are group means with standard deviations.

DISCUSSION

The increase in respiration rate by prostaglandin has not been previously recorded. The mechanism is not obvious, although in similarly prepared animals drug-induced hypotension is commonly associated with an increase in respiratory rate (Maxwell, Elliott & Kneebone, 1962; Maxwell, Robertson & Elliott, 1963). The increase in minute volume of respiration compares with that found in studies of PGE_1 in humans (Bergström *et al.*, 1965). This increase in respiratory exchange may be relevant to the decreases in blood carbon dioxide values now recorded; the increase in oxygen consumption (previously recorded in man by Bergström *et al.*, 1965) and the change in carbon dioxide production are similar. Accordingly, the whole-body exchange-ratio did not change significantly. The narrowing of the whole-body oxygen extraction (arterial—mixed venous oxygen difference), and the increase in whole-body oxygen consumption each contribute to the calculated increase in cardiac output. This result is not unexpected in a compound with vasodilating properties (cf. von Euler, 1937); the finding is, however, directly opposed to the report of a decrease in cardiac output in humans given prostaglandin (Bergström, Dunér, Euler, Pernow & Sjövall, 1959). The difference in the response of cardiac output between the study cited (Bergström *et al.*, 1959) and the present one may represent a species-difference, or perhaps a response to the higher dose of PGE_1 now given.

The acceleration of heart-rate agrees with the studies of others in man (Bergström *et al.*, 1959), and animals (Carlson and Orö, 1966), as does the decrease in systemic blood pressure. There was a reasonable inverse correlation between these two responses ($R = -0.4976$; $P<0.05$). This relationship, noted by Marey in resting conditions would seem to be the product of baroreceptor activity (Wright, 1962). Both cardiac output and heart-rate increased, the latter more so ; thus the stroke volume decreased.

The decrease in systemic pressure, when related to the increase in cardiac output, must of course lead mathematically to a decrease in total peripheral resistance. Again, this is not unexpected when it is recalled that early studies of prostaglandin demonstrated vasodilation in the frog leg (von Euler, 1937). The increase in cardiac output more than offsets the decrease in systemic pressure so that left ventricular work is maintained. As in the human (Bergström *et al.*, 1959), the change in pulmonary arterial pressure was small and transient (Fig. 1) ; the increase in cardiac output was the principal association in the decrease of calculated total pulmonary resistance, and the increase of right ventricular work.

In general then, the effects of PGE_1 on the general haemodynamics are to decrease blood pressure and to increase cardiac output and heart rate. Most of these responses accord with the opinions of previous workers, and may add weight to the findings concerning coronary blood flow and myocardial metabolism.

The increase in mean coronary flow is of the order of 40%. It is felt that this is physiologically as well as statistically significant. It should be recalled that the method used measures mean coronary flow/100 g of left ventricle over 10 min. Rapid changes in coronary flow may not be detected. The increase in coronary flow found parallels that for the total cardiac output. The change in calculated coronary vascular resistance is similar in trend to the changes in total peripheral and pulmonary resistances. The increase in coronary flow showed a positive correlation with the increase in heart-rate ($R = 0.6799$; $P<0.01$), and an inverse correlation with systemic blood pressure change ($R = -0.5082$; $P<0.02$). These correlations are of course associative and not necessarily causal, although it is known that tachycardia of itself may cause an increase in coronary flow (cf. Maxwell, Castillo, White, Crumpton & Rowe, 1958).

There is no previous information concerning the effect of PGE_1 upon myocardial oxygen and carbon dioxide metabolism. The decline in coronary sinus oxygen content is a principal contribution to the widening of the cardiac oxygen extraction (arterial—coronary sinus oxygen difference) ; the changes in myocardial carbon dioxide production are similar in trend. Accordingly the cardiac respiratory quotient is unchanged. The increase in cardiac oxygen consumption (coronary flow times the arterial–coronary sinus oxygen difference) is due rather to the increase in coronary flow (+40%) than the change in cardiac oxygen extraction (+19%). The same conclusions apply to the changes in myocardial carbon dioxide exchange. The cardiac oxygen consumption is high in relation to left ventricular work. Accordingly, cardiac efficiency is reduced.

It has been said (Bergström *et al.*, 1966) that PGE_1 may in some circumstances stimulate the sympathetic system ; the results for the coronary circulation are somewhat against this conclusion, since such activity is usually associated with an increase in coronary sinus oxygen content (Maxwell, Rowe, Castillo, Clifford, Afonso & Crumpton, 1960 ; Granata, Olsson, Huvos & Gregg, 1965). The profile of coronary vascular response is not characteristic of β-receptor blockade (Maxwell *et al.*, 1963), nor of blockade of the

sympathetic ganglia (Crumpton, Rowe, O'Brien & Murphy, 1954). In general, both the cardiac and general haemodynamic effects recall those of bradykinin (Maxwell *et al.*, 1962).

The biochemical changes are of some interest; the results for NEFA are characteristic of those recorded by others for high doses of PGE_1 (Bergström *et al.*, 1966). The lowering effect, not surprisingly, is also seen in the coronary sinus blood; the absolute myocardial extraction decreased (arterial–coronary sinus NEFA difference, 0.20 to 0.12 m-equiv/l.) although the change did not reach a statistically significant value. The percentage NEFA extraction $\left(\frac{\text{arterial–coronary sinus}}{\text{arterial}} \times 100\right)$ showed little change (43% to 38%). The decline in glucose values is statistically, and possibly physiologically, significant. This finding contrasts with the report of Bergström *et al.* (1966). Again the high dose used in the present study may partially explain this difference in result. Myocardial glucose extraction was not significantly changed. There are no reports on the effects of PGE_1 on arterial lactate or pyruvate levels. Accordingly, these results cannot be compared with those of others. The increase in coronary sinus lactate, while statistically significant, is of dubious physiological import. The change in extraction of lactate by the heart failed to achieve statistical significance ($0.67>P>0.5$). There was a remarkable decrease in arterial pyruvate, with a subsequent significant change in the arterial lactate/pyruvate ratio (9.5 to 18.0). As in exercise in humans (Harris, Bateman & Gloster, 1962), there was a suggestion of a positive correlation between the increase in ventilation produced by PGE_1 and the lactate/pyruvate ratio ($R=0.3831$, $0.1>P>0.05$): The parallel decreases in glucose and arterial pyruvate, suggests, but does not prove, that whole-body carbohydrate metabolism is affected by PGE_1.

The general spectrum of biochemical change (decrease in glucose, NEFA) is somewhat reminiscent of an insulin effect (Hales & Randle, 1963). However, in two studies, assay by radiobiological methods for insulin-like activity in blood revealed no change from control. Presumably these biochemical changes described are due to PGE_1, and not to a secondary release of insulin.

In general, then, prostaglandin E_1, in high doses, can dilate the systemic, pulmonary, and coronary vascular systems; whole-body and cardiac oxygen consumption increases, and cardiac efficiency declines. These haemodynamic changes coincide with a decrease in blood glucose and NEFA values.

SUMMARY

1. In 10 intact, anaesthetized dogs, cardiac output, vascular pressures, coronary flow, glucose, NEFA, lactate, and pyruvate levels, were measured before and after an infusion (average 1.5 μg/kg/min) of prostaglandin E_1.

2. Comparison with control studies showed a significant increase in respiratory rate, respiratory exchange, cardiac output, and heart rate. Systemic pressure decreased, as did systemic and pulmonary vascular resistances.

3. Coronary flow increased, as did myocardial oxygen extraction and cardiac oxygen usage. Cardiac efficiency decreased, as did coronary vascular resistance.

4. Blood glucose and NEFA decreased, so did arterial pyruvate values.

5. Prostaglandin E_1 is a potent vasodilator of the circulatory beds studied; it does not appear to have sympathomimetic effects, nor are the changes noted those of ganglionic blockade or β-adrenergic block. In general, the changes resemble those of a more complex vasoactive polypeptide such as bradykinin.

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