Br. J. Pharmac. (1976), **57**, 533–541

INTERACTIONS OF ISOPRENALINE AND PROSTAGLANDIN E_2 WITH RESPECT TO MYOCARDIAL CONTRACTILE FORCE, CORONARY VASCULAR RESISTANCE AND MYOCARDIAL OXYGEN CONSUMPTION IN GUINEA-PIG ISOLATED HEARTS

R. KREBS & K. SCHRÖR

Department of Pharmacology, University of Mainz, Obere Zahlbacher Str. 67, 65 Mainz, West Germany

1 Left ventricular pressure (LVP), left ventricular pressure derivative (LV dp/dt_{max}), coronary vascular resistance (CVR) and myocardial oxygen consumption (Q_{O_2}) were measured simultaneously in isolated, electrically driven hearts of guinea-pigs at constant perfusion rate.

2 LVP, LV dp/dt_{max}, CVR and Q_{O_2} were greatly decreased by either the addition of prostaglandin E_2 (50 ng/ml) to the perfusion fluid or pretreatment of the animals with reserpine.

3 Isoprenaline (0.5 nM to 100 nM) induced increases in LVP, LV dp/dt_{max} and Q_{O_2}. In the presence of prostaglandin E_2, there was a parallel shift of the isoprenaline concentration-response curve for LVP and LV dp/dt_{max}. This effect was not seen, after the animals had been treated with reserpine.

4 Q_{O_2} was also decreased by prostaglandin E_2 only in non-reserpine treated animals.

5 CVR was diminished by isoprenaline in the untreated group. However, there was increase in CVR, when isoprenaline was added to either prostaglandin E_2 or reserpine-pretreated hearts which was enhanced in the reserpine plus prostaglandin E_2-treated group ($P < 0.01$).

6 The results give evidence for different actions of prostaglandin E_2 on isoprenaline concentration-response curves for LVP, LV dp/dt_{max} and CVR.

Introduction

Both prostaglandin E_1 and E_2 inhibit the overflow of noradrenaline as well as inotropic and chronotropic responses following sympathetic nerve stimulation in the isolated perfused heart of the rabbit, while prostaglandin $F_{2\alpha}$ is ineffective (Hedqvist & Wennmalm, 1971). In the same study no influence of these compounds on the effects of exogenously added noradrenaline was observed and a mainly presynaptic action of E type prostaglandins was assumed. However, these results were only partially confirmed by Baum & Shropshire (1971) and Bhagat, Dhalla, Ginn, LaMontagne & Montier (1972), whereas Dhalla & Balasubramanian (1972) found prostaglandin E_2 had no influence on release, but inhibited uptake of [^{3}H]-noradrenaline in the rat heart. Thus, the results are conflicting with respect to the mechanism of interaction between noradrenaline and prostaglandins of the E-series.

The effects of isoprenaline on the performance of the dog heart and the myocardial fibrillation threshold of the cat were found to be inhibited by the addition of prostaglandin E_2 (Schrör & Forster, 1974; and unpublished), but not by prostaglandin $F_{2\alpha}$ (Förster, Schrör & Weiss, 1975). This could be taken as evidence for post-junctional inhibition by prostaglandin E_2 of catecholamine-induced increase in myocardial performance and excitability, since isoprenaline is assumed not to be inactivated by neuronal uptake mechanisms (Bönisch & Trendelenburg, 1974). However, in whole animal experiments, the participation of endogenous catecholamines, even with respect to the effects of isoprenaline, cannot be excluded.

Hence, the interaction between isoprenaline and prostaglandin E_2 on myocardial performance was studied in isolated heart preparations when the heart rate was held constant. In order to prevent limitations of oxygen availability, especially at high isoprenaline concentrations, P_{O_2} was measured in the venous effluent in addition to coronary vascular resistance. Because it became evident from earlier studies on the same model, that the effects of prostaglandin E_2 are closely dependent on the endogenous catecholamine content of the preparations (Krebs & Schrör, 1975a; 1975b; Schrör & Krebs, 1975), the experiments were performed in both reserpine-treated and non-reserpine-treated animals.

Methods

Heart preparations

In guinea-pigs of either sex (300–400 g body weight) thoracotomy was performed under light ether anaesthesia after pretreatment with heparin (10 mg/kg i.p.). After the aorta and pulmonary artery had been cannulated, all other vessels near the heart were ligated and the heart placed in the perfusion apparatus.

During the experiments the heart was perfused at constant flow via a metallic aortic cannula with Tris buffered Tyrode solution (pH 7.4) containing 1.8 mM Ca^{2+}, equilibrated with 95% O_2 and 5% CO_2 at 32°C and electrically stimulated through the aortic cannula at a constant rate of 180 beats/min (Grass stimulator S5, impulse duration 4 ms, 40 V).

Mean coronary perfusion pressure was measured by Statham P 23 Bb pressure transducer in the aorta, immediately distal to the aortic valves and was considered to be a direct expression of coronary vascular resistance (CVR), since the perfusion rate was held constant.

Myocardial oxygen consumption (Q_{O_2}) was calculated from the oxygen partial pressure in the pulmonary artery outflow, as measured by polarography, using platinum electrodes (Clark principle) (Klaus & Krebs, 1969).

A fluid filled rubber balloon catheter was inserted into the left ventricle through the mitral ostium for measurement of left ventricular actively developed pressure (LVP) and left ventricular dp/dt_{max} (LV dp/dt_{max}) using a Statham P 23 Db pressure transducer. Left ventricular diastolic pressure was zero. Under these experimental conditions changes in the LVP, as measured by the compression of the balloon, are therefore assumed to be a direct expression of alterations in the left ventricular afterload.

Design of the experiments

Two series of experiments were performed. The animals of the first series served as controls and were divided into three groups. The animals of the first group received no drugs and were used to study the time of constant performance of the preparations. The second group of animals were pretreated with reserpine (7 mg/kg i.p. once 16–24 h prior to surgery), and then checked for the degree of depletion in the cardiac catecholamine stores by addition of tyramine 1 μg/ml (final concentration) to the bath fluid. The hearts of the third group were also pretreated with reserpine in the same way and then incubated with indomethacin at a final concentration of 0.16 μg/ml, to obtain information on the possible role of endogenous prostaglandin-like substances for myocardial performance and Q_{O_2}.

The animals of the second series ($n=64$) were divided into 2 groups. The first group ($n=38$) was pretreated with reserpine as described above. The second group ($n=26$) was not pretreated. Half the animals from each group were randomly selected for treatment with prostaglandin E_2. After the preparations had been stabilized, isoprenaline sulphate was added in a cumulative way (0.5, 1, 5, 10, 50 and 100 nM) in the presence or absence of prostaglandin E_2 (final concentration 50 ng/ml perfusion fluid). In earlier investigations, in which the prostaglandin E_2 concentration-response curve was studied using these parameters and the same model, this concentration was found to be maximally active (Krebs & Schrör, 1975b).

Experiments were started after an equilibration period of about 30 min and did not last longer than 90 minutes.

Drugs

The following drugs were used: tyramine chloride (Merck), isoprenaline sulphate (Boehringer, Ingelheim), reserpine (Serpasil, CIBA), prostaglandin E_2 (Prostin E_2, Upjohn) and indomethacin (Sharp & Dohme). Stock solutions of prostaglandin E_2 were prepared as follows: 5 mg was dissolved in 0.5 ml 95% ethanol; 4.5 ml Na_2CO_3 (20 mg/100 ml) was added, the final pH checked (6–7.5) and the solution stored frozen at −25°C for not longer than 1 month. From this stock a more dilute solution, containing 5 μg/ml prostaglandin E_2 was prepared, immediately before the experiment, and an aliquot was added to the perfusion fluid to give the final concentration required.

Statistical analysis

Statistical evaluation was performed using the *t*-test for non-paired observations. The mean and standard error ($\bar{x} \pm$ s.e. mean) are quoted in the text. The level of significance for α was 0.01.

For the isoprenaline concentration-response relationship, a two-way regression analysis for dependent observations was made over the log-linear part of the respective concentration-response curve, by computing the coefficient of correlation (*r*), slope (*b*), intercept on the y axis (*a*) and the 95% confidence interval (programme MED 00 402, Prof. J. Berger, Institut für Medizinische Statistik und Dokumentation der Universität Mainz). *n* is the number of observations.

Results

First series of experiments

Time of constant performance of the preparations. In the first group of this series, LVP

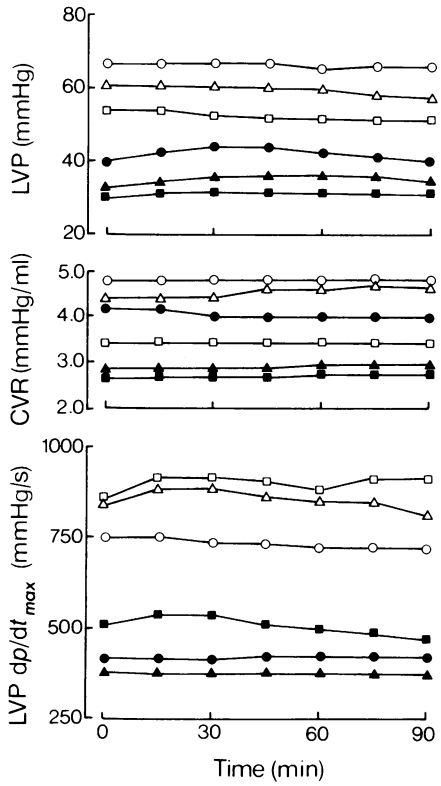

Figure 1 Changes in LVP, CVR and LV dp/dt_{max} in 3 reserpine-treated (closed symbols) and 3 non-reserpine-treated (open symbols) guinea-pigs as a function of time. Measurements were made every 15 min after stabilization (time 0) of the preparation.

(mmHg), LV dp/dt_{max} (mmHg/s), CVR (mmHg/ml) and Qo_2 (µl O_2 per g ventricular dry weight/min) were checked for constancy over a time period of 90 min after stabilization of the preparations in non-reserpine-treated ($n=3$) and reserpine-treated ($n=3$) animals. No changes in any of these parameters in dependence on the time were observed ($P>0.01$). The respective results for LVP, LV dp/dt_{max} and CVR for each animal are shown in Figure 1. Note the influence of reserpine-treatment. Thus, at least for this period, it may be assumed that the heart preparations maintain a stable performance under our experimental conditions.

Degree of depletion of the cardiac noradrenaline stores by reserpine pretreatment. The actual degree of catecholamine depletion by reserpine pretreatment was checked in another group of this series, when the heart preparations were given tyramine at a final concentration of 1 µg/ml ($n=8$). As summarized in Table 1, there were essentially no changes in any of the parameters measured, when the respective values before and in the presence of tyramine were compared ($P>0.01$). Thus, sufficient depletion of the cardiac noradrenaline stores may be assumed.

Actions of indomethacin. In order to obtain information on the possible role of endogenous prostaglandin-like substances for myocardial performance and Qo_2, indomethacin at a final concentration of 0.16 µg/ml was added to the bath fluid of 7 reserpine-pretreated heart preparations. By this procedure, the LVP was altered to 35 ± 2 mmHg (before: 36 ± 2), the LV dp/dt_{max} to 468 ± 35 mmHg/s (before: 441 ± 24) and the Qo_2 to 250 ± 20 µl O_2 per g ventricular dry weight/min (before: 247 ± 22). Thus these parameters were not affected by the presence of indomethacin ($P>0.01$). The same was true for the solvent ethanol (final concentration 0.01 vol.%). Increase of the indomethacin-concentration up to 0.5 µg/ml in 3 additional experiments was also without any effect on these parameters, thus providing evidence that endogenous prostaglandin-like substances are not involved in the maintenance of myocardial performance or Qo_2 in these animals.

Second series of experiments

Actions of prostaglandin E_2 in non-reserpine-treated group. Table 2 shows that prostaglandin E_2

Table 1 LVP (mmHg), LV dp/dt_{max} (mmHg/s), CVR (mmHg/ml) and Qo_2 (µl O_2 per g ventricular dry wt./min) in reserpine-pretreated animals before (control) and in presence of 1 µg/ml tyramine (tyramine)

Group	*LVP*	*LV dp/dt_{max}*	*CVR*	Qo_2
Control	40 ± 3	477 ± 28	3.25 ± 0.27	246 ± 17
Tyramine	43 ± 3	567 ± 46	3.31 ± 0.28	256 ± 17
% change	+7.5	+18.9	+1.8	+4.1
Significance	NS	NS	NS	NS

$n=8$. The means, standard errors ($\bar{x} \pm$ s.e. mean) and the percentage change caused by tyramine (control = 100%) are given. Level of significance for α: 0.01.

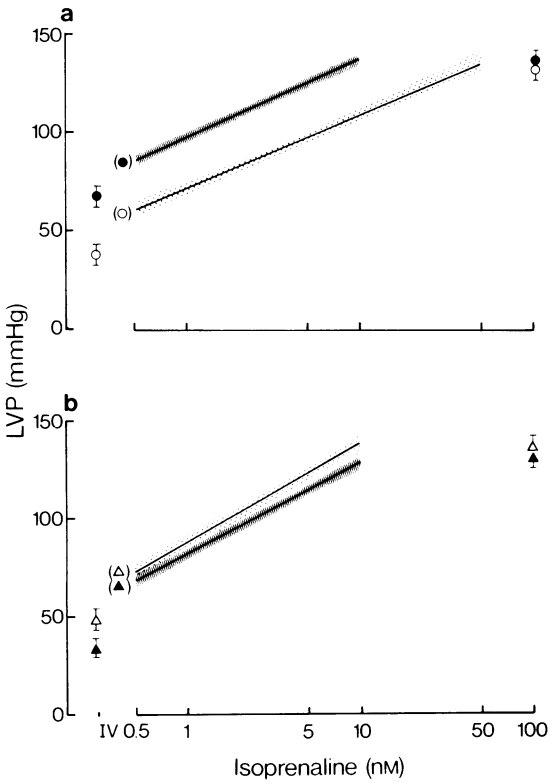

Figure 2 Isoprenaline concentration-response curve for LVP in (a) non-reserpine-treated and (b) reserpine-treated animals in the presence (open symbols) or absence (closed symbols) of 50 ng/ml prostaglandin E_2. The log-linear part of the concentration-response curve with the 95% confidence limit is given. The respective initial values (IV) and values at 100 nM isoprenaline ($\bar{x} \pm$ s.e. mean) are also indicated. $n=56$ (●); $n=55$ (○); $n=72$ (▲); $n=72$ (△).

(50 ng/ml) leads to a marked decrease in LVP, LV dp/dt_{max}, CVR and $\dot{Q}O_2$ ($P<0.01$). Moreover, it is noticeable, that the decrease in LVP, LV dp/dt_{max} and CVR is as much as 40–50% of the control values, whereas $\dot{Q}O_2$ is only diminished by 17%.

Actions of prostaglandin E_2 in the reserpine-pretreated group. Reserpine-treatment itself diminished LVP and LV dp/dt_{max} as well as CVR and $\dot{Q}O_2$ significantly by about 41, 52, 32 and 31%, respectively (non-prostaglandin E_2-treated groups in Tables 2 and 3). Prostaglandin E_2 (50 ng/ml) produced no further decrease in myocardial mechanics, but rather increased LVP and LV dp/dt_{max}, 23 and 30%, respectively; increases which were not statistically significant ($P>0.01$). $\dot{Q}O_2$ was also not altered, but the CVR diminished to almost the same extent as in the non-reserpine-treated group, i.e. by 32.7%, when compared with the respective initial value ($P<0.01$) (Table 3).

Isoprenaline concentration-response curves. The isoprenaline concentration-response curves for LVP, LV dp/dt_{max}, CVR and $\dot{Q}O_2$ as influenced by prostaglandin E_2, reserpine pretreatment or both prostaglandin E_2 and reserpine pretreatment are shown in Figures 2–5. The respective isoprenaline concentration-response curves with the 95%-confidence limit are given as obtained by computer analysis for the log-linear part of each curve. The initial values immediately before addition of isoprenaline and the final values at 0.1 μM (100 nM) ($\bar{x} \pm$ s.e. mean) are also given; n refers to the number of observations for the log-linear part of the isoprenaline concentration-response curve.

Left ventricular pressure. Addition of isoprenaline was followed by a concentration-dependent increase in LVP up to a final value of 130–140 mmHg, which was essentially the same for all groups ($P>0.01$), despite the different initial values. For the non-

Table 2 Changes in LVP (mmHg), LV dp/dt_{max} (mmHg/s), mean CVR (mmHg/ml) and $\dot{Q}O_2$ (μl O_2 per g ventricular dry wt./min) without and in presence of prostaglandin E_2 (PGE_2) 50 ng/ml in non-pretreated animals

Group	*LVP*	*LV* dp/dt_{max}	*CVR*	$\dot{Q}O_2$
No PGE_2	66 ± 4	965 ± 52	4.05 ± 0.24	396 ± 21
Plus PGE_2	39 ± 4	498 ± 42	2.45 ± 0.21	329 ± 20
% change	−41.9	−48.4	−39.5	−16.9
Significance	+	+	+	+

$n=12$. The means, standard errors ($\bar{x} \pm$ s.e. mean) and the percentage change by prostaglandin E_2 (no $PGE_2=100\%$) are given. Level of significance for α: 0.01.

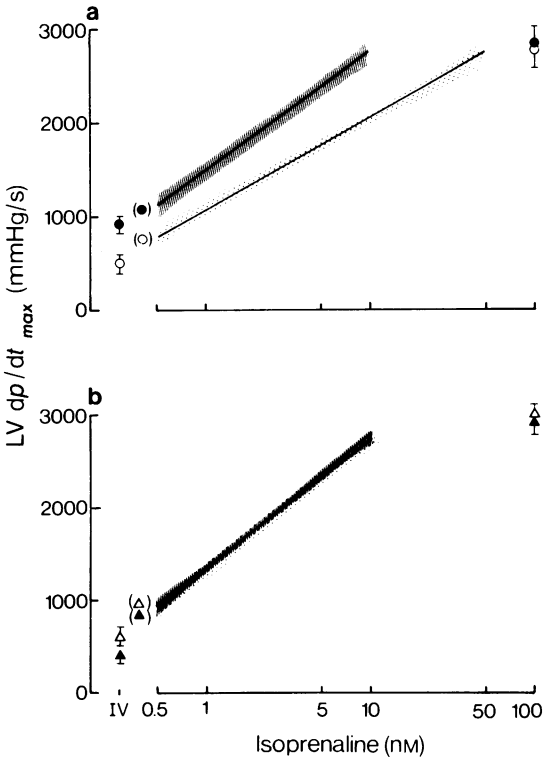

Figure 3 Isoprenaline concentration-response curve for LV dp/dt_{max} in (a) non-reserpine-treated and (b) reserpine-treated animals in the presence (open symbols) or absence (closed symbols) of 50 ng/ml prostaglandin E_2. The log-linear part of the concentration-response curve with the 95% confidence limit is given. The respective initial values (IV) and values at 100 nM isoprenaline ($\bar{x} \pm$ s.e. mean) are also indicated. $n=56$ (●); $n=55$ (○); $n=72$ (▲); $n=72$ (△).

reserpine-treated group, a plateau was reached at 10 nM isoprenaline, which, in presence of prostaglandin E_2 (50 ng/ml) was only seen after 50 nM isoprenaline, thereby shifting the concentration-response curve to the right in a parallel manner, as confirmed statistically by comparing the slope and the confidence limits for both groups (Figure 2, circles).

After pretreatment with reserpine, the isoprenaline concentration response curve was essentially unchanged, whether prostaglandin E_2 was present or not (Figure 2, triangles). Furthermore as seen for the non-reserpine-treated animals not treated with prostaglandin E_2, concentrations of isoprenaline greater than 10 nM caused no further increase in LVP.

Left ventricular pressure derivative (LV dp/dt_{max}). Addition of isoprenaline was also followed by a concentration-dependent increase in LV dp/dt_{max} up to a final value of 2900–3000 mmHg/s, which was essentially the same for all groups ($P > 0.01$), despite the different initial values.

In the non-reserpine-treated group a plateau was again observed at 10 nM isoprenaline, which in the presence of prostaglandin E_2 was only found after 50 nM isoprenaline was added, thereby shifting the concentration-response curve in a similar manner as shown for LVP (Figure 3, circles).

After pretreatment with reserpine, no further influence by prostaglandin E_2 on the isoprenaline-induced increase in LV dp/dt_{max} was found. Again, there was no further change in this parameter, in the presence of concentrations greater than 10 nM isoprenaline, whether prostaglandin E_2 was present or not (Figure 3, triangles).

Coronary vascular resistance (CVR). As seen with myocardial contractile force there were also concentration-dependent changes in CVR induced by isoprenaline. Both the slope and degree of these

Table 3 Changes in LVP (mmHg), LV dp/dt_{max} (mmHg/s), mean CVR (mmHg/ml) and Qo_2 (µl O_2 per g ventricular dry wt./min) without and in presence of prostaglandin E_2 (PGE_2) 50 ng/ml in reserpine-treated animals

Group	*LVP*	*LV dp/dt_{max}*	*CVR*	Qo_2
No PGE_2	39 ± 3	465 ± 38	2.76 ± 0.31	272 ± 15
Plus PGE_2	48 ± 4	605 ± 51	1.86 ± 0.15	279 ± 14
% change	+23.0	+30.1	−32.7	+2.5
Significance	NS	NS	+	NS

$n=19$. The means, standard errors ($\bar{x} \pm$ s.e. mean) and the percentage change by prostaglandin E_2 (no $PGE_2 = 100\%$) are given. Level of significance for α: 0.01.

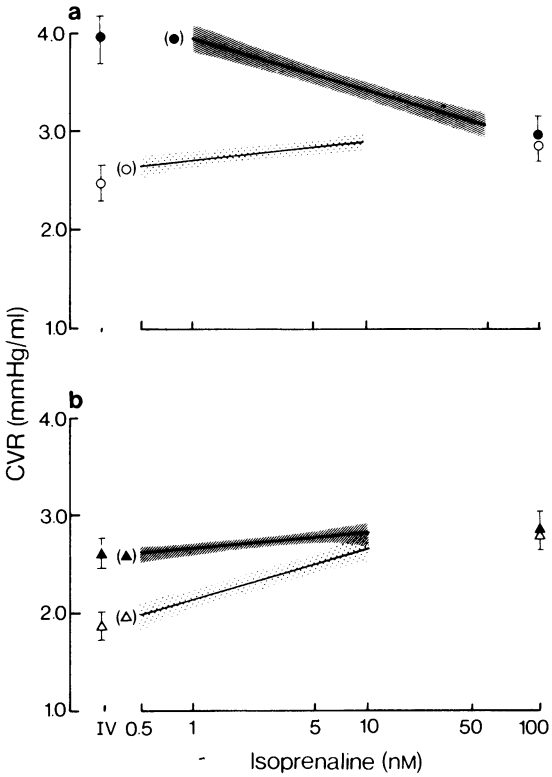

Figure 4 Isoprenaline concentration-response curve for CVR in (a) non-reserpine-treated and (b) reserpine-treated animals in presence (open symbols) or absence (closed symbols) of 50 ng/ml prostaglandin E_2. The log-linear part of the concentration-response curve with the 95% confidence limit is given. The respective initial values (IV) and values at 100 nM isoprenaline ($\bar{x} \pm$ s.e. mean) are also indicated. $n=48$(●); $n=44$ (○); $n=72$ (▲); $n=43$ (△).

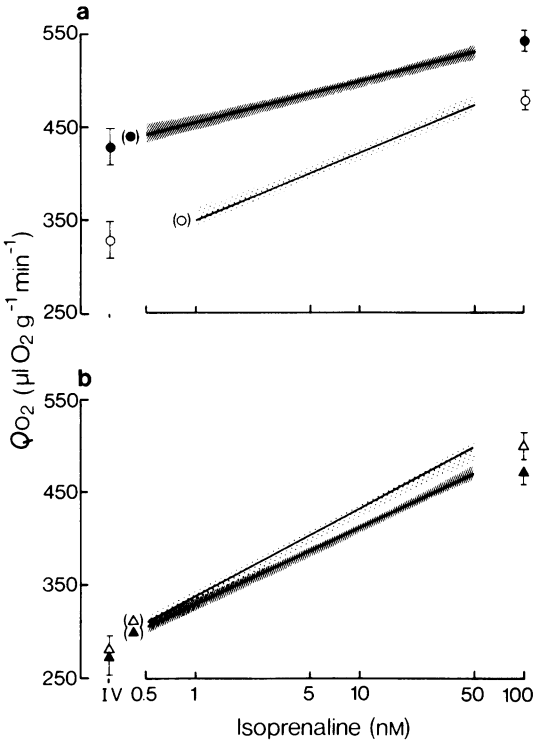

Figure 5 Isoprenaline concentration-response curve for Qo_2 (µl O_2 per g ventricular dry wt./min) in (a) non-reserpine-treated and (b) reserpine-treated animals in presence (open symbols) or absence (closed symbols) of 50 ng/ml prostaglandin E_2. The log-linear part of the concentration-response curve with the 95% confidence limit is given. The respective initial values (IV) and values at 100 nM isoprenaline ($\bar{x} \pm$ s.e. mean) are also indicated. $n=70$ (●); $n=44$ (○); $n=90$ (▲); $n=90$ (△).

alterations were quite different in the single experimental groups, however, very good agreement between all means in CVR were observed at maximum isoprenaline concentration, ranging between 2.78–2.96 mmHg/ml ($P > 0.01$).

Isoprenaline in the non-reserpine-treated group led to a marked decrease in CVR in concentrations of 1 nM to 50 nM by about 25%. In contrast to that, the presence of prostaglandin E_2 caused a small but significant increase in CVR, when isoprenaline was added in concentrations between 0.5 nM to 10 nM ($P < 0.01$). The marked influence of prostaglandin E_2 alone should be noted (see also Table 2) (Figure 4, circles).

Isoprenaline in reserpine-treated animals produced essentially the same increase in CVR as shown in presence of prostaglandin E_2 for non-reserpine-treated animals (Figure 3, closed triangles). However, this increase was significantly greater, if prostaglandin E_2 was also present, starting at the absolutely lowest level measured in these experiments, i.e. 1.86 ± 0.15 mmHg/ml (Figure 4, open triangles).

Myocardial oxygen consumption (Qo_2). Isoprenaline caused concentration-dependent increases of Qo_2 in all groups.

In the non-reserpine-treated animals isoprenaline produced greatest Qo_2, i.e. 544 ± 12 µl per g ventricular

dry wt./min at the concentration of 100 nM. In the presence of prostaglandin E_2 this concentration-response relationship was altered significantly: elevations in $\dot{Q}O_2$ were obtained first at 1 nM isoprenaline and the curve shifted downwards, i.e. the maximum $\dot{Q}O_2$ at 100 nM isoprenaline was only 483 ± 12 µl per g ventricular dry wt./min ($P < 0.01$) (Figure 5, circles).

After the animals had been treated with reserpine, no further influence of prostaglandin E_2 on the isoprenaline concentration-response curve could be detected (Figure 5, triangles). However, it should be noted, that the maximum $\dot{Q}O_2$ for the reserpine plus isoprenaline treated group (isoprenaline concentration 100 nM) is only 469 ± 9 µl per g ventricular dry wt./min, i.e. significantly lower than without previous reserpine-treatment ($P < 0.01$).

The PO_2 in the efflux of the pulmonary artery under all conditions was higher than 200 mmHg.

Discussion

A parallel shift in isoprenaline-induced increase in LVP and LV dp/dt_{max} could be observed in non-pretreated animals, thus confirming earlier results, obtained *in situ*, where prostaglandin E_2 was found to inhibit isoprenaline-induced changes in myocardial performance (Schrör & Förster, 1974) and fibrillation threshold (Schrör & Förster, unpublished). However, the isoprenaline concentration-response curve for LVP and LV dp/dt_{max} remained essentially unchanged, whether prostaglandin E_2 was present or not in reserpine-treated animals. These differing results support the assumption, that prostaglandin E_2 does not directly influence these isoprenaline concentration-response relationships but indirectly, through a factor which is removed by previous reserpine-treatment.

Much evidence suggests this factor is the endogenous catecholamine content of the heart. As shown by the addition of tyramine, there is adequate depletion of cardiac catecholamine stores by reserpine-treatment. According to this, there is also a sharp drop in myocardial contractile force produced by reserpine-treatment, which is also found after prostaglandin E_2 is added, but only in non-reserpine-treated animals. Indomethacin treatment did not alter contractile force or $\dot{Q}O_2$ in reserpine-treated animals, indicating that endogenous prostaglandin-like substances should not mask any intrinsic contractile action of prostaglandin E_2.

Therefore the endogenous catecholamines seem to be involved in maintenance of cardiac performance in non-pretreated animals. Most probably, the electrical stimulation of the heart through the aortic cannula leads also to stimulation of cardiac sympathetic fibres, thereby liberating noradrenaline, if present. Stimulation frequencies of 3 Hz with square wave impulses of less than 5 ms duration are well known to induce liberation of noradrenaline (Junstadt & Wennmalm, 1973). However, at the low current of about twice threshold strength, there may be no exhaustion of catecholamine stores, as seen from the constant performance of the preparations in the experiments of the first series.

The inability of prostaglandin E_2 to inhibit actions of isoprenaline in catecholamine-depleted animals supports the view that, with respect to left ventricular pressure development and dp/dt_{max}, there is no post-junctional interaction between isoprenaline and prostaglandin E_2. Hence, the shift in the isoprenaline concentration-response curve for the myocardial contractile force in non-reserpine-treated animals could be explained in terms of prejunctional inhibition of noradrenaline release by prostaglandin E_2. Interestingly, this mechanism seems to be operative up to the highest isoprenaline concentrations, in essentially the same manner, because these curves are parallel. Thus, one may assume that endogenous noradrenaline is not only involved in the maintenance of cardiac performance under control conditions but also under conditions of enhanced myocardial activity, because isoprenaline is known not to undergo presynaptic reuptake (Bönisch & Trendelenburg, 1974) and thus should not interfere directly with presynaptic noradrenaline release or reuptake.

This hypothesis is supported by the result, that the isoprenaline concentration-response curve seems to be shifted in a similar way both by reserpine-treatment and by prostaglandin E_2 in non-reserpine-treated animals. Furthermore, prostaglandin E_2 decreased LVP and LV dp/dt_{max} in a concentration-dependent fashion only in control, but not in reserpine-treated animals (Krebs & Schrör, 1975b). Finally, such effects could be obtained only with prostaglandin E_2 but not with $F_{2\alpha}$ (Schrör & Krebs, 1975), in agreement with observations *in situ* (Förster, Schrör & Weiss, 1975). In contrast to prostaglandin E_2, $F_{2\alpha}$ is assumed to exert no effect on nerve-stimulation-induced increase in myocardial performance by interaction with prejunctional mechanisms (Hedqvist, 1973).

On the other hand, a decrease in CVR induced by prostaglandin E_2 was found in both reserpine-treated and non-treated groups, giving further evidence for a different action of prostaglandin E_2 on myocardial contractile force and CVR.

This additional relaxing effect of prostaglandin E_2 in the reserpine-treated group could be explained by further reduction of some residual catecholamine release or by a direct dilating action of the prostaglandin. This effect was concentration-dependent (Krebs & Schrör, 1975b) and the release of noradrenaline was shown to be only partially inhibited by prostaglandin E_2 (Hedqvist & Wennmalm, 1971), arguments in favour of a direct relaxing action.

In agreement with the observations of Bassenge,

Walter & Doutheil (1967), initial vascular tone had a considerable influence on the coronary actions of catecholamines. Accordingly, isoprenaline decreased CVR only if the initial tone was high, i.e. in the non-reserpine-treated group, but could produce a slight increase, if the tone was reduced by either reserpine or prostaglandin E_2. At the lowest level of CVR, i.e. 1.86 mmHg/ml in the reserpine plus prostaglandin E_2-treated group, this increase was significantly more pronounced, than with prostaglandin E_2 or reserpine alone. This could be explained by an influence of intramural pressure, which in our experimental conditions is only detectable, if the vascular component of coronary resistance is negligibly low. On the other hand, Trendelenburg (1974) in experiments on the isolated nictitating membrane found isoprenaline to act via both α-(contraction) and β-(relaxation) adrenoceptors and the reaction to be markedly dependent on the initial contractile state of the preparation. As coronary arteries are assumed to possess both β- and α-adrenoceptors (Zuberbuhler & Bohr, 1965) the different actions of isoprenaline on CVR as influenced by prostaglandin E_2 and reserpine may be understood on the basis of enhanced α-adrenergic activity under conditions of low coronary vascular tone.

There is no evidence that either CVR or myocardial contractile force was affected by hypoxia. The Po_2 in the effluent under all experimental conditions was higher than 20 mmHg, which strongly suggests that sufficient oxygen was available to the heart. Alterations in Qo_2, therefore, resembled the changes in LVP and LV dp/dt_{max} in many respects, in particular the isoprenaline concentration-dependent increase and the shift of those curves by prostaglandin E_2 in only non-reserpine-treated animals. The same is true for the respective initial values. However, striking differences are also detectable.

The increases in LVP and LV dp/dt_{max}, produced by isoprenaline in the non-reserpine-treated group were 100% and 209% over the initial value, respectively. On the other hand, the Qo_2 was only enhanced by about 27%. Similar results, greater alterations in contractile force than in the oxygen demands, were also found for the other groups, including changes after reserpine-treatment or prostaglandin E_2 alone.

This work was supported by the Deutsche Forschungsgemeinschaft. The authors wish to thank Dr F. Brunnberg, The Upjohn Company, for kindly supplying prostaglandin E_2.

References

BASSENGE, E., WALTER, P. & DOUTHEIL, U. (1967). Wirkungsumkehr der adrenergischen Coronargefäßreaktion in Abhängigkeit vom Coronargefäßtonus. *Pflügers Arch.*, **297**, 146–155.

BAUM, T. & SHROPSHIRE, A.T. (1971). Influence of prostaglandins on autonomic responses. *Amer. J. Physiol.*, **221**, 1470–1475.

BHAGAT, R., DHALLA, N.S., GINN, D., LA MONTAGNE, A.E. & MONTIER, A.D. (1972). Modification by prostaglandin E_2 (PGE_2) of the response of guinea-pig isolated vasa deferentia and atria to adrenergic stimuli. *Br. J. Pharmac.*, **44**, 689–698.

BÖNISCH, H. & TRENDELENBURG, U. (1974). Extraneuronal removal, accumulation and O-methylation of isoprenaline in the perfused heart. *Naunyn-Schmiedebergs Arch. Pharmak.*, **283**, 191–218.

DHALLA, N.W. & BALASUBRAMANIAN, V. (1972). Effect of prostaglandins and cyclic AMP on ^{3}H-norepinephrine transport across adrenergic neurons in heart. Abst. *5th Int. Congr. Pharmacol.*, San Francisco, p. 80.

FÖRSTER, W., SCHRÖR, K. & WEISS, M. (1975). Wechselwirkungen zwischen den Prostaglandinen E_2 und $F_{2\alpha}$ und Isoprenalin am Hundeherzen in situ. *Acta biol. med. germ.*, **34**, 501–506.

HEDQVIST, P. (1973). Autonomic neurotransmission. In *The Prostaglandins*, Vol. 1, ed. Ramwell, P.W., pp. 101–103. New York: Plenum Press.

HEDQVIST, P. & WENNMALM, Å. (1971). Comparison of the effects of prostaglandins E_1, E_2 and $F_{2\alpha}$ on the sympathetically stimulated rabbit heart. *Acta physiol. scand.*, **83**, 156–162.

JUNSTADT, M. & WENNMALM, Å. (1973). Prostaglandin mediated inhibition of noradrenaline release at different nerve impulse frequencies. *Acta physiol. scand.*, **89**, 544–549.

KLAUS, W. & KREBS, R. (1969). Über die Abhängigkeit der Strophanthineinwirkung auf den myocardialen Sauerstoffverbrauch vom Funktionszustand des Herzens. *Naunyn-Schmiedebergs Arch. Pharmak.*, **264**, 337–353.

KREBS, R. & SCHRÖR, K. (1975a). Different actions on isolated atrial and ventricular myocardium of guinea pig by PGE_2. Influence of reserpinization, isoprenaline and variations in Ca_e^{++}. *Naunyn-Schmiedebergs Arch. Pharmak.*, **287**, Suppl. R 29.

KREBS, R. & SCHRÖR, K. (1975b). Actions of prostaglandin E_2 on myocardial mechanics, coronary vascular resistance and oxygen consumption in the guinea pig isolated heart preparation. *Br. J. Pharmac.*, **55**, 403–408.

SCHRÖR, K. & FÖRSTER, W. (1974). Interactions between isoproterenol and prostaglandin E_2 in the dog heart in situ. *Pol. J. Pharmac.*, **26**, 143–149.

SCHRÖR, K. & KREBS, R. (1975). Actions of PGE_2 and $PGF_{2\alpha}$ on contractile force, coronary flow and oxidative metabolism of isolated hearts of guinea pig and rabbit. *Abstr. Intern. conference on prostaglandins*, Florence, p. 121.

TRENDELENBURG, U. (1974). An analysis of the alpha and beta effects of isoprenaline on the isolated, nictitating membrane. *Naunyn-Schmiedebergs Arch. Pharmak.*, **285**, 375–393.

ZUBERBUHLER, R.C. & BOHR, D.F. (1965). Responses of coronary smooth muscle to catecholamines. *Circulation Res.*, **16**, 431.

(Received January 5, 1976)