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Inotropic Effects of Prostaglandin D₂ and E₁ on the Newborn Rabbit Heart

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ABSTRACT. This study determines the inotropic effects of prostaglandin D₂ (PGD₂) and prostaglandin E₁ (PGE₁) in the isolated, arterial perfused newborn (NB) and adult (A) rabbit heart.

Significant positive inotropism of PGD₂ was observed at all concentrations studied (1×10^{-17} to 1×10^{-7} M) in the two age groups; the effect in the NB was significantly greater ($p < 0.05$) than that in the A at PGD₂ concentrations higher than 1×10^{-17} M. Significant positive inotropism of PGE₁ was observed at PGE₁ concentrations higher than 1×10^{-8} M in the NB, and only at 1×10^{-6} M in the A.

In the NB, the relaxation parameters [$1/2$ RT and the ratio of $+dT/dt$ (max) to $-dT/dt$ (max)] decreased to 80% of control after PGE₁ infusion, but not after PGD₂ infusion. In contrast, relaxation parameters in the A were not different from control.

Propranolol (1×10^{-6} M) did not alter the positive inotropic action of PGD₂ and PGE₁ in the NB. These data indicate that: 1) the positive inotropic effects of PGD₂ and PGE₁ in NB are greater than that in the A, 2) PGE₁ and not PGD₂, enhances myocardial relaxation only in the NB,

3) the contractile effects of PGD₂ and PGE₁ are not mediated by β -receptors. (*Pediatr Res* 18:1277-1281, 1984)

Abbreviations

PGE₁, prostaglandin E₁
PGD₂, prostaglandin D₂
DT, developed tension
RT, resting tension
 $+dT/dt$ (max), maximal rate of tension development
 $-dT/dt$ (max), maximal rate of relaxation
 $1/2$ RT, half-relaxation time

PGE₁ has been used to maintain the patency of the ductus arteriosus in the newborn with ductus-dependent congenital heart disease (9). Recent studies in fetal and newborn lambs (5, 32) showed that PGD₂ decreased the pulmonary arteriolar resistance and suggested that PGD₂ may be used to treat newborns with persistent pulmonary hypertension (5, 32). However, little is known about the inotropic effects of prostaglandins in the newborn. Previous reports of the influence of PGs on myocardial contractility in the adult are inconsistent (18, 19). These contradictory results may be due to heart rate variability (4, 34), extracellular Ca²⁺ concentration [Ca²⁺] (20), species (4, 19), and the experimental preparation (19, 34).

This study was designed to determine the action of PGE₁ and

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PGD₂ on myocardial mechanical function in arterially perfused newborn and adult rabbit hearts.

MATERIALS AND METHODS

Experimental Preparation. Experiments were performed utilizing the isolated arterially perfused septum of newborn (4–7 days old) and adult (6–12 months old) New Zealand White rabbits. The details of this preparation have been described previously (12). In brief, the rabbit was heparinized (150 units/kg body weight) and anesthetized with sodium pentobarbital (50 mg/kg body weight). After thoracotomy, the heart was rapidly excised. The septal branch of the left coronary artery was then cannulated with PE-50 polyethylene. A Harvard pump was used to perfuse the septum with an oxygenated Krebs-Henseleit solution at a constant flow rate (2.5 ml/g tissue/min) throughout the experiment. The right and left ventricular free walls were trimmed away. The base of the septum was suspended by a silk suture from a force transducer (Statham UC4).

The muscle was paced at 36 beats/min and its temperature was maintained at $27 \pm 0.5^\circ\text{C}$. This temperature was chosen because we have shown that both mechanical function and myocardial high energy phosphates (12, 13) as well as tissue potassium and calcium concentrations remain constant for 6 h during control perfusion (25). Tension was measured using a Statham force transducer and a bridge amplifier (Accudata 113, Honeywell, Inc., Denver, CO). The first derivative of tension with respect to time was derived using an analog differentiator (Accudata 132, Honeywell, Inc.). The following parameters of mechanical function were monitored with a Brush 220 recorder (Gould, Cleveland, OH): DT, RT, $+dT/dt$ (max), $-dT/dt$ (max), and $\frac{1}{2}RT$. The ratio of $+dT/dt$ (max) to $-dT/dt$ (max) was calculated as a parameter of myocardial relaxation (10, 29).

Solutions. The control solutions contained in mM: NaCl, 118; CaCl₂, 1.5; glucose, 6; KCl, 6.0; MgCl₂, 1; NaHCO₃, 24; and NaH₂PO₄, 0.435. The solution was equilibrated with 95% O₂, 5% CO₂. The oxygen content in the control solution was 1.9–2.2 vol % by Lex-O₂-Con (Lexington Instruments) determinations. The pH and PCO₂ ranged from 7.30 to 7.40 and from 35 to 45 mm Hg, respectively.

Indomethacin (Merck, Sharpe and Dohme) was freshly prepared by dissolving the powder in ethanol (10 mg/ml) and an aliquot was added to the perfusate to achieve final indomethacin concentration of 1×10^{-6} M. Propranolol hydrochloride (Ayerst Pharmaceutical Co.) was suspended in the perfusate to achieve final concentration of 1×10^{-6} M.

Isoproterenol bitartrate (Sigma Co.) was suspended in the perfusate to achieve final concentration of 1×10^{-8} M.

PGD₂ and PGE₁ were purchased from Upjohn (Kalamazoo, MI) in dry form. These drugs were dissolved in 100% ethanol (10 mg/ml) and stored at -20°C . An aliquot was added to the perfusate to achieve final concentrations of 10^{-17} to 10^{-7} M PGD₂ and 10^{-8} to 5×10^{-6} M PGE₁. An aliquot of 100% ethanol solution was also added to the control perfusate to achieve the same concentration as the perfusate containing PGs. All solutions containing PGs were prepared within 15 min of administration.

Experimental Protocol. Muscles were perfused initially with a control solution for 60 min to allow for stabilization of mechanical function. After this period the following studies were performed.

PGD₂. The effect of PGD₂ on myocardial mechanical function

was studied in the newborn ($n = 26$), and the adult ($n = 27$) rabbit. The muscle was perfused with a solution containing 1×10^{-17} M, 1×10^{-15} M, 1×10^{-13} M, 1×10^{-11} M, 1×10^{-9} M, or 1×10^{-7} M of PGD₂ for 60 min ($n = 4$ –5 at each concentration).

PGE₁. The effect of PGE₁ on myocardial mechanical function was studied in the newborn ($n = 22$) and the adult ($n = 20$) rabbit. The muscle was perfused with a solution containing 1×10^{-8} M, 1×10^{-7} M, 1×10^{-6} M, or 5×10^{-6} M of PGE₁ for 10 min ($n = 4$ –6 at each concentration).

Indomethacin. In additional experiments, the effects of PGD₂ and PGE₁ on mechanical function in the newborn were studied in the presence of indomethacin (1×10^{-6} M) in the perfusate. This concentration of indomethacin has been shown to inhibit myocardial production of PGE₁ (22). The muscle was perfused with a solution containing 1×10^{-6} M indomethacin for 30 min. The muscle was then perfused with solutions containing PGD₂ (1×10^{-11} M) plus indomethacin (1×10^{-6} M), or PGE₁ (1×10^{-6} M) plus indomethacin (1×10^{-6} M).

Propranolol. The effects of PGD₂ and PGE₁ on mechanical function were studied in the presence of propranolol (1×10^{-6} M). The muscle of the newborn was perfused for 10 min with the solution containing 1×10^{-6} M propranolol. The muscle was then perfused with solution containing PGD₂ (1×10^{-11} M) plus propranolol (1×10^{-6} M) or PGE₁ (5×10^{-6} M) plus propranolol (1×10^{-6} M). To confirm the effect of propranolol as a β -antagonist, the muscle was perfused with solutions containing isoproterenol (1×10^{-8} M).

Results were expressed as the mean $\pm$ standard error. Statistical analysis was performed with unpaired and paired Student's *t* test; a *p* value of <0.05 was considered significant. The paired Student's *t* test was used to determine the significance of the inotropic effect of PGE₁ and PGD₂ in each experiment.

RESULTS

The control values of myocardial mechanical function in the newborn and adult are shown in Table 1. The values of DT, RT, $+dT/dt$ (max), $-dT/dt$ (max), $\frac{1}{2}RT$, and the ratio of $+dT/dt$ (max) to $-dT/dt$ (max) in the newborn were not significantly different from those in the adult. Ethanol and indomethacin had no significant effects on mechanical function.

The results of a typical experiment in the newborn are shown in Figure 1. The maximal inotropic effects obtained at each PGD₂ and PGE₁ concentration are presented in Figures 2 and 3, respectively. A significant positive inotropic effect of PGD₂ was observed at all concentrations studied in the two age groups; the augmented contractility in the newborn was significantly greater ($p < 0.05$) than in the adult for concentrations higher than 10^{-17} M. Significant inotropism of PGE₁ was observed at PGE₁ concentrations higher than 1×10^{-8} M in the newborn, and only at 1×10^{-6} M in the adult. At PGE₁ concentrations of 1×10^{-6} M, and 5×10^{-6} M, the increases in the $+dT/dt$ (max) in the newborn were significantly greater ($p < 0.03$) than that in the adult.

The dose-response curve for PGD₂ and PGE₁ is shown in Figure 4. Only PGE₁ increased contractility with increasing concentrations, and this effect was observed only in the newborn (Fig. 4).

Figure 5A shows the time course of the effect of PGD₂ infusion. $+dT/dt$ (max) reached its peak value at 5 min in the adult and

Table 1. The baseline data obtained before perfusion of prostaglandins*

Age	<i>n</i>	DT (g/g wet wt)	RT (g/g wet wt)	$+dT/dt$ (max) (g/s/g wet wt)	$-dT/dt$ (max) (g/s/g wet wt)	$\frac{1}{2}RT$ (ms)	$+dT/dt$ (max)/ $-dT/dt$ (max)
Newborn	48	7.3 ± 0.4	1.8 ± 0.1	30.7 ± 1.9	18.7 ± 1.3	306 ± 11	1.64 ± 0.05
Adult	44	7.9 ± 0.4	1.6 ± 0.1	30.6 ± 1.5	18.2 ± 1.0	326 ± 10	1.69 ± 0.03

* Values are mean $\pm$ SE.

Fig. 1. Typical effect of PGE₁ (left) and PGD₂ (right) on the tension and tension first derivative (dT/dt).

Fig. 2. The inotropic effect of PGD₂ in the newborn and adult rabbit heart. The values represent the mean $\pm$ SEM. * $p < 0.05$ = significant difference between the mean values in the newborn and the adult.

Fig. 3. The inotropic effect of PGE₁ in the newborn and adult rabbit heart. The values represent the mean $\pm$ SEM. * $p < 0.05$ = significant difference between the mean values in the newborn and the adult.

50 min in the newborn; the maximal value in the newborn was significantly greater ($p < 0.05$) than in the adult. Figure 5B shows the time course of $+dT/dt$ (max) during PGE₁ infusion. $+dT/dt$ (max) reached plateau at 5 min of PGE₁ infusion in the adult and at 10 min in the newborn. Half-relaxation time (Fig. 6) and

Fig. 4. The dose-response curve for PGD₂ (upper panel) and PGE₁ (lower panel) in the newborn (○) and adult (●). Note that the inotropic effect was only dose dependent for PGE₁ and only in the newborn.

Fig. 5. Time course of the effect of PGD₂ (A) and PGE₁ (B) on maximal rate of tension development [$+dT/dt$ (max)]. * $p < 0.05$ = significant difference between the mean values in the newborn and adult.

Fig. 6. The effect of PGD₂ and PGE₁ on $\frac{1}{2}$ RT in the newborn and adult rabbits. * $p < 0.05$, ** $p < 0.01$ = significant difference between the mean values in the newborn and adult.

Fig. 7. The effect of PGD₂ and PGE₁ on $+dT/dt(\max)/-dT/dt(\max)$ in the newborn and adult rabbits. * $p < 0.05$ = significant difference between the mean values in the newborn and adult.

$+dT/dt(\max)/-dT/dt(\max)$ ratio (Fig. 7) did not change significantly after PGD₂ infusion in the two age groups. In muscles perfused with PGE₁ at concentrations higher than 1×10^{-8} M, both $\frac{1}{2}$ RT and $+dT/dt(\max)/-dT/dt(\max)$ ratio decreased significantly ($p < 0.05$) in the newborn, but not in the adult (Figs. 6 and 7).

Effects of PGD₂ in low calcium. Additional PGD₂ experiments were performed to determine the effect of low extracellular calcium (0.5 mM) on the inotropic effect of PGD₂ (1×10^{-11} M) in the adult. The absolute increase in $+dT/dt(\max)$ in muscles perfused with low calcium (3.31 ± 0.37 g/s/g wet wt) was similar to that found in muscles perfused with 1.5 mM calcium (2.41 ± 0.70 g/s/g wet wt) but the per cent increase was significantly greater ($p < 0.05$) at the lower calcium concentration (19 ± 2 at 0.5 mM Ca²⁺ versus 6 ± 2 at 1.5 mM Ca²⁺).

Inotropic effects of PGD₂ and PGE₁ in propranolol. Additional experiments were performed to determine the effect of β -antagonist on the inotropic actions of PGD₂ and PGE₁ in the newborn. In muscles perfused with isoproterenol (1×10^{-8} M), $+dT/dt(\max)$ increased to $121 \pm 8\%$ of control and the values were not significantly different from those obtained with PGD₂ and PGE₁. Propranolol (1×10^{-6} M) completely blocked the positive inotropic effect of isoproterenol (1×10^{-8} M), and did not alter the positive inotropic effect of PGD₂ and PGE₁. Propranolol did not

alter PGE₁ and PGD₂ effects on $\frac{1}{2}$ RT and the $+dT/dt(\max)/-dT/dt(\max)$ ratio.

PGD₂ and PGE₁ effects were unchanged when indomethacin was added to the solution.

DISCUSSION

Previous reports on the inotropic effects of prostaglandins are not consistent. Using the Langendorf preparation of the adult, Schror (31) showed that PGD₂ did not change mechanical function in the guinea pig, while Karmazyn *et al.* (15) demonstrated that PGD₂ increased myocardial contractile force in the rat. PGE₁ augments contractility in the cat (34) and dog (1, 7) papillary muscles, and in the frog ventricular strips (3). However, others have found that PGE₁ had no inotropic effect in the adult cat and dog (33), and in the kitten (16).

The reasons for these contradictory results are not clear. Because PGE₁ dilates and PGD₂ constricts the coronary arteries (15, 19, 31), these drugs may alter myocardial oxygen supply and consequently contractility. The present study showed that both PGE₁ and PGD₂ had positive inotropic effects, and in the adult, these effects are enhanced at low extracellular Ca²⁺ concentrations. The higher apparent inotropism at low extracellular Ca²⁺ has been reported previously by us (11, 25, 27) and other investigators (20).

In the present study, the positive inotropism of PGE₁ was associated with a decrease in $\frac{1}{2}$ RT and $+dT/dt(\max)/-dT/dt(\max)$ ratio. This effect of PGE₁ is similar to that of isoproterenol and dibutyl-*c*-AMP administration reported by Nishioka *et al.* (27) and others (2, 10, 29) and suggests that PGE₁ inotropism may be mediated by the adenylate cyclase-*c*-AMP system (14, 24).

PGE₁ activates myocardial adenylate cyclase (14, 16, 17), but does not inhibit phosphodiesterase (17), while propranolol has no effect on this action (16, 17). The fact that propranolol did not alter the PGE₁ effect suggests that PGE₁ action is not mediated by β -receptors and might be due to stimulation of cyclic AMP.

The present study demonstrates that PGD₂ had no effect on the relaxation parameters in the newborn and adult (Figs. 6 and 7). This suggests that the mechanisms of PGD₂ and PGE₁ actions are different. The propranolol experiments also suggest that the effect of PGD₂ is not mediated by β -receptors.

The present study showed that the maximal inotropic effects of PGD₂ and PGE₁ in the newborn were significantly greater than in the adult (Figs. 2 and 3). Tissue calcium content in the newborn is less than in the adult, and equal increments of tissue calcium causes a greater increase in $+dT/dt(\max)$ in the newborn (11, 25, 27). The greater inotropic action of PGs in the newborn may be explained by lower intracellular calcium in the newborn (11). The time course of the inotropic effect of PGs in the two age groups were different (Fig. 5), and low [Ca²⁺]_o did not alter this course. Because the time course of various inotropic agents which increases calcium influx (11, 15) are similar in the two age groups, the age-related difference in the time course observed in the present study cannot be explained by calcium-mediated differences *per se*. In the newborn, both enhanced inotropism, and shortening of the relaxation time after PGE₁ infusion were greater than in the adult (Figs. 3 and 6). Nishioka *et al.* (27) showed that isoproterenol infusion caused comparable reductions in $\frac{1}{2}$ RT in newborn and adult rabbit. Furthermore, Cheng *et al.* (6) showed that isoproterenol stimulation of adenylate cyclase in fetal and adult sheep heart was similar. Thus, the attenuated effect of PGE₁ in the adult myocardium cannot be explained by a decreased sensitivity of the adenylate cyclase-*c*-AMP system. Because subcellular organelles (*i.e.* sarcolemma, sarcoplasmic reticulum, mitochondria, and myofibrils) are involved in excitation-contraction coupling and their functions vary with development (8, 26, 28, 30), the effect of PGs on subcellular function may be different in the newborn and adult.

In addition, developmental changes may exist in myocardial PG metabolism (diffusion of PGs into the cell, PG catabolism, etc.) and this may cause age-related differences in myocardial contractility.

In summary, the present data indicate that both PGD_2 and PGE_1 have positive inotropic effects, but only PGE_1 promotes myocardial relaxation. The inotropic actions of PGD_2 and PGE_1 in the newborn are greater than in the adult.

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