Effects of 8-Isoprostaglandin E_1 on the Systemic and Pulmonary Circulations in Dogs[1] (34679)

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Recently Daniels *et al.* (1) biosynthetized a new isomer of prostaglandin E_1 (PGE_1), 8-isoprostaglandin E_1 (8-iso-PGE_1), and confirmed its chemical structure (Fig. 1). Weeks *et al.* (2) reported that 8-iso-PGE_1 has very low biological activity relative to PGE_1. The hypotensive action of 8-iso-PGE_1 is approximately one-tenth that of PGE_1 in dogs and cats. Otherwise, little information is presently available on the cardiovascular effects of 8-iso-PGE_1. The present study was undertaken to investigate the effects of 8-iso-PGE_1 on the systemic and pulmonary circulations and to compare them with those of PGE_1 and prostaglandin $F_{2\alpha}$.

Methods. Twenty-one dogs, weighing between 15 and 22 kg, were anesthetized with sodium pentobarbital (30 mg/kg). The techniques used to study the cardiovascular effects of 8-iso-PGE_1 have been described previously (3–5). In all experiments the left hemithorax was opened under artificial respiration. The pericardium was incised, and the heart was suspended in a pericardial cradle. Sodium heparin (2.5 mg/kg) was given intravenously every 0.5 hr. Systemic and pulmonary arterial pressures were measured continuously with Statham pressure transducers (P23AA) connected to catheters placed in the left subclavian artery, through the left mammary artery and in the pulmonary artery through a small branch of the left pulmonary artery. Heart rate and myocardial contractile force were measured continuously with an Electronics for Medicine (EFM) tachometer (model TDC-1) and with a Wal-

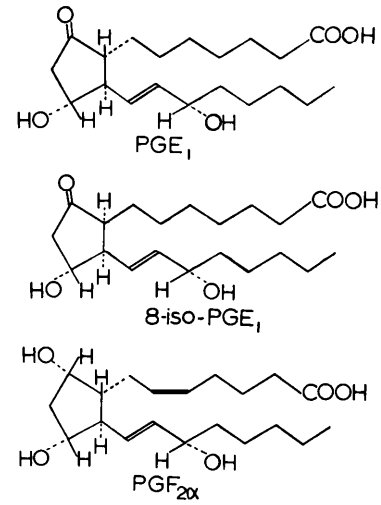

FIG. 1. Chemical structure of prostaglandin E_1 (PGE_1), 8-isoprostaglandin E_1 (8-iso-PGE_1) and prostaglandin $F_{2\alpha}$ ($PFG_{2\alpha}$).

ton-Brodie strain gauge arch sutured directly to the right ventricular muscle. In 7 dogs blood was directed from the inferior vena cava, through a femoral vein into the cannulated left pulmonary artery, and blood flow in the left pulmonary artery was kept constant by means of a Sigmamotor pump (model TM2). The pulmonary arterial perfusion pressure was measured continuously with a Statham pressure transducer (P23AA). The hemodynamic parameters measured, except heart rate, were continuously recorded with an EFM research recorder (model DR 8) or a Grass polygraph (model 7). PGE_1, 8-iso-PGE_1, and $PGF_{2\alpha}$ were obtained from Dr. J. Pike, Upjohn Co., Kalamazoo, Michigan. The purity of each prostaglandin was confirmed with thin-layer chromatography, using one of the solvent systems (A IX) described previ-

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ously (6). Each prostaglandin was dissolved in 95% ethanol (1 mg/ml) and further diluted with 0.9% NaCl solution to make a 100 μg/ml solution prior to the intra-arterial (ia) or intravenous (iv) injection to the dogs. The data in this paper were evaluated statistically, employing the *t* test (7).

Results. The cardiovascular effects of the iv administration of geometrically increasing doses (0.25 to 16 μg/kg) of PGE$_1$, 8-iso-PGE$_1$, and PGF$_{2\alpha}$ were studied in 21 dogs. The results are summarized in Fig. 2. As reported previously from this laboratory (5, 8, 9), the iv administration of 0.25 to 4 μg/kg of PGE$_1$ decreased mean systemic arterial pressure and increased heart rate, mean pulmonary arterial pressure, and myocardial contractile force essentially in proportion to the dose. On the other hand, the iv administration of 1 to 8 μg/kg of PGF$_{2\alpha}$ increased mean systemic and pulmonary arterial pressures and myocardial contractile force (8, 10).

The effects of the iv administration of 1 to 16 μg/kg of 8-iso-PGE$_1$ on heart rate, mean systemic and pulmonary arterial pressures, and myocardial contractile force were qualitatively similar to those of PGE$_1$. However, the magnitude of the systemic hypertensive effect of 8-iso-PGE$_1$ was approximately 1/125 to 1/250 that of PGE$_1$, while the pulmonary hypertensive effect of 8-iso-PGE$_1$ was approximately 5 times that of PGE$_1$ (Fig. 2).

The mechanism of the effect of 8-iso-PGE$_1$ on the pulmonary circulation was studied in 7 additional dogs in which the left pulmonary arterial blood flow was kept constant with a Sigmamotor pump. The results are summarized in Table I, and a representative experiment is illustrated in Fig. 3. The ia injection of a single dose (2 μg/kg) of PGE slightly decreased the pulmonary arterial perfusion pressure, indicating that it dilates the pulmonary vascular bed (Fig. 3). On the other hand, the ia injection of the same dose of either PGF$_{2\alpha}$ or 8-iso-PGE$_1$ increased it markedly, indicating that they constricted the pulmonary vascular beds (Fig. 3). The magnitude of the pulmonary hypertensive effect of PGF$_{2\alpha}$ is approximately twice that of 8-iso-PGE$_1$.

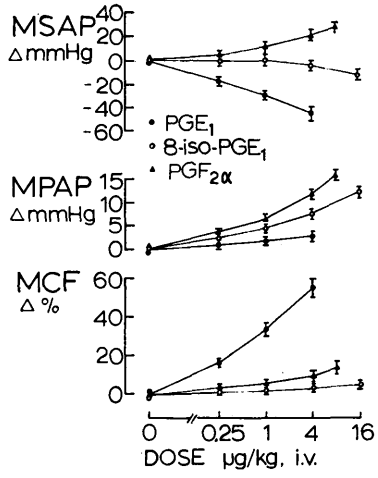

FIG. 2. Effects of the iv administration of graded doses (0.25–16 μg/kg) of PGE$_1$, 8-iso-PGE$_1$, and PGF$_{2\alpha}$ on mean systemic arterial pressure (MSAP), mean pulmonary arterial pressure (MPAP) and myocardial contractile force (MCF) in 21 dogs: (●, ○, ▲) represent average effects (± SEM) on the different parameters in 7 dogs.

Discussion. It was shown previously that PGE$_1$ decreased systemic arterial pessure, whereas PGF$_{2\alpha}$ increased it in dogs (5, 8–10). On the other hand, both PGE$_1$ and PGF$_{2\alpha}$

TABLE I. Effects of the Intrapulmonary Arterial Injection of a Single Dose (2 μg/kg) of 8-Isoprostaglandin on Heart Rate, Mean Systemic Arterial Pressure, Mean Pulmonary Arterial Pressure and Myocardial Contractile Force in Dogs in Which Pulmonary Arterial Blood Flow Was Kept Constant by Means of a Sigmamotor Pump.

Hemodynamic parameters	Control	8-Iso-PGE$_1$ (2 μg/kg)
Heart rate (beats/min)	151 ± 5	152 ± 5
Mean systemic arterial pressure (mm Hg)	146 ± 6	142 ± 7
Mean pulmonary arterial pressure (mm Hg)	11.4 ± 0.4	21.5 ± 0.8[a]
Myocardial contractile force (g)	112 ± 8	114 ± 7

[a] Significant ($p < 0.05$).

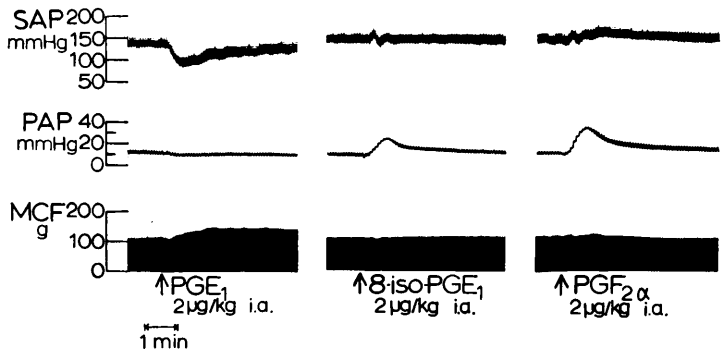

FIG. 3. Effects of the ia pulmonary artery administration of a single dose (2 μg/kg) of PGE$_1$, 8-iso-PGE$_1$, and PGF$_{2\alpha}$ on the systemic arterial pressure (MSAP) and the perfusion pressure in the left pulmonary artery (MPAP) of a dog in which left pulmonary arterial blood flow was kept constant by a Sigmamotor pump through the period of the experiment.

increased pulmonary arterial pressure, although the magnitude is much smaller with PGE$_1$ than with PGF$_{2\alpha}$. From the results obtained in the present study, it is evident that 8-iso-PGE$_1$ decreases systemic arterial pressure and increases heart rate and myocardial contractile force in anesthetized dogs. The magnitudes of these actions by 8-iso-PGE$_1$ are considerably smaller than those by PGE$_1$. In addition, both PGE$_1$ and 8-iso-PGE$_1$ increased pulmonary arterial pressure. However, the magnitude of this action is markedly greater with 8-iso-PGE$_1$ than with PGE$_1$. Previously Bergström *et al.* (11) and Nakano and Cole (10) showed that the systemic hypotensive action of the iv administration of PGE$_1$ is considerably smaller than that of the administration of PGE$_1$ into the aorta or the left atrium. This was ascribed mainly to degradation of PGE$_1$ in the lungs by an enzyme, 15-hydroxyprostaglandin dehydrogenase (PGDH) (12). The less potent systemic hypotensive action of 8-iso-PGE$_1$ observed in this study, however, may not be due mainly to the degradation by PGDH in the lungs. Very recently Nakano *et al.* (13) found that the *Km* value of 8-iso-PGE$_1$ for PGDH is considerably greater than that of PGE$_1$, indicating that 8-iso-PGE$_1$ is a less favorable substrate than PGE$_1$ for PGDH.

It appears that 8-iso-PGE$_1$ is a unique prostaglandin with respect to its cardiovascular actions. The effects of 8-iso-PGE$_1$ on the heart and systemic circulation resemble those of PGE$_1$, whereas the effect of 8-iso-PGE$_1$ on the pulmonary circulation resembles that of PGF$_{2\alpha}$. Daniels *et al.* (1) demonstrated that when bis-homo-gamma-linoleic acid was incubated with mammalian seminal vesicle homogenates, approximately 90% of prostaglandins produced was PGE$_1$, and the remaining 10% was 8-iso-PGE$_1$. There is no documentation in regard to the isolation and biological action of 8-iso-PGE$_1$ *in vivo* as yet. However, it is reasonable to assume that 8-iso-PGE$_1$ would also be present in seminal plasma and exert some biological actions in different species of animals.

Summary. The effects of 8-iso-prostaglandin E$_1$ on the systemic and pulmonary circulations were studied and compared with those of PGE$_1$ and PGF$_{2\alpha}$ in anesthetized dogs. It was found that the iv administration of 8-iso-PGE$_1$ decreased systemic arterial pressure slightly and increased heart rate and myocardial contractile force slightly. The magnitude of the systemic hypotensive effect of 8-iso-PGE$_1$ was equivalent to approximately 1/125 to 1/250 of that of PGE$_1$ in dogs. On the other hand, the pulmonary hypertensive action of 8-iso-PGE$_1$ was 5 times greater than that of PGE$_1$. The present study indicates that 8-iso-PGE$_1$ increases pulmonary arterial pressure through its vasoconstrictor action on the pulmonary vascular bed.

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