Hemodynamic Effects of Prostaglandins E_1, A_1 and $F_{2\alpha}$ in Dogs* (32937)

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Although extensive studies have been made on the biochemical characterizations of the different prostaglandins (1–3), rather scanty information is presently available in regard to the cardiovascular effects of prostaglandins, and the hemodynamic mechanism of their actions (1,4–6). It was found that prostaglandin E_1 (PGE_1) decreases systemic arterial pressure, and increases heart rate and cardiac output in dogs and rats (1,4,6). On the other hand, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) was found to increase systemic and pulmonary arterial pressures, and cardiac output in dogs (5). Practically no studies have been made on the hemodynamic effects of prostaglandin A_1 (PGA_1). The present study was undertaken to elucidate further the precise effects of the three prostaglandins on the cardiovascular dynamics in dogs.

Methods. Twenty-one dogs were anesthetized with the intravenous (i.v.) administration of sodium pentobarbital (30 mg/kg). Systemic, pulmonary arterial, left and right atrial pressures were measured continuously with Statham pressure transducers (P23AA and P23D). Heart rate, myocardial contractile force, and cardiac output were measured continuously with an Electronics for Medicine (EFM) tachometer (TDC-1), a Walton-Brodie strain gauge arch (7,8) and a Shipley-Wilson rotameter (9) as described previously (10–12). Total and pulmonary peripheral resistances were calculated from the following formulas: Total peripheral resistance (mm Hg/ml per min) = mean systemic arterial pressure (mm Hg)/cardiac output (ml/min). Pulmonary peripheral resistance (mm Hg/ml per min = [mean pulmonary arterial pressure (mm Hg) — mean left atrial pressure (mm Hg)]/cardiac output (ml/min). Prostaglandins used in this study are crystalline preparations which were dissolved with pure ethanol, to a 1 mg/ml stock solution, and diluted further with a 0.9% NaCl solution to make a 40 or 100 μg/ml solution. Prostaglandins were given to dogs intravenously every 15–20 min. The data in this paper were evaluated statistically, employing the *t* test (13).

Results. The effects of the i.v. administration of graded doses (0.25–8.0 μg/kg) of PGE_1, PGA_1 and $PGF_{2\alpha}$ on the cardiovascular dynamics were studied in 21 dogs. The results are summarized in Fig. 1, and tracings from representative experiments are illustrated in Fig. 2. As seen in Fig. 2 (Upper Tracing), the i.v. injection of 4.0 μg/kg of PGA_1 increased heart rate, mean pulmonary arterial pressure, myocardial contractile force, and cardiac output; the maximum increases were 14 beats/min, 3 mm Hg, 43.9%, and 15.8%, respectively. On the other hand, PGA_1, decreased mean left atrial pressure and mean systemic arterial pressure, the maximum reductions were 2.2 and 36 mm Hg, respectively. Both calculated systemic and pulmonary peripheral resistances decreased significantly. The hemodynamic changes caused by PGA_1 usually returned to control values within approximately 15 min. As shown in Fig. 1, the hemodynamic changes induced by PGE_1 were qualitatively similar to those induced by PGA_1, but the magnitude of the former was slightly greater than the latter. In contrast, as shown in Fig. 2 (Lower Tracing), the i.v. administration of 8.0 μg/kg of $PGF_{2\alpha}$ increased systemic arterial pressure, pulmonary arterial pressure, myocardial contractile force, and cardiac output, the maximum increments amounting to 18 mm Hg, 10 mm Hg, 23%, and 10%, respectively. Both calculated total and pulmonary peripheral resistances increased significantly. As seen in Fig. 2, the changes in cardiac output were multiphasic; an initial, slight increase being followed by a transient return to a control value before a second, greater and

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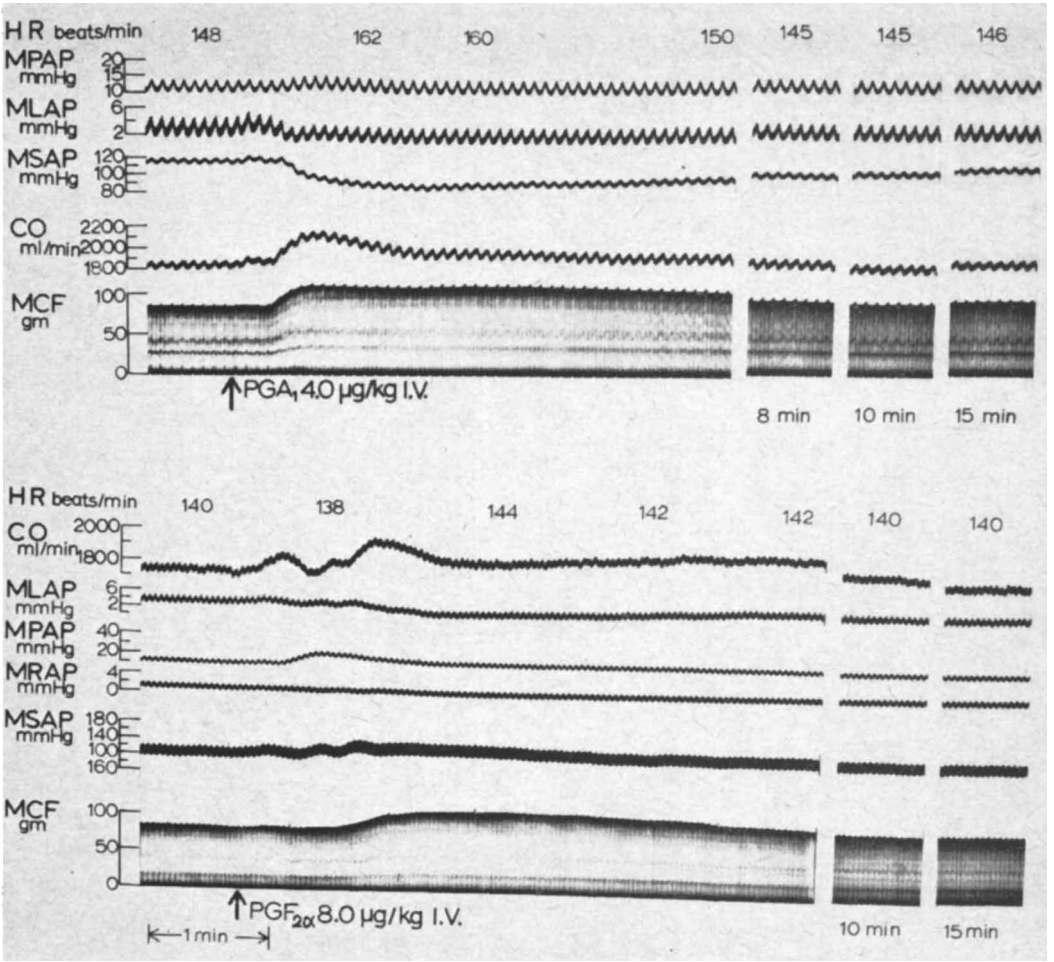

FIG. 1. Upper Tracing: The effects of the i.v. administration of 4.0 µg/kg of PGA, on heart rate (HR), mean pulmonary arterial pressure (MPAP), mean left artial pressure (MLAP), mean systemic arterial pressure (MSAP), cardiac output (CO), and myocardial contractile force (MCF) in a dog. Lower Tracing: The effects of the i.e. administration of 8.0 µg/kg of $PGF_{2\alpha}$ on heart rate (HR), cardiac output (CO), mean left atrial pressure (MLAP), mean pulmonary arterial pressure (MPAP), mean right atrial pressure (MRAP), mean systemic arterial pressure. (MSAP), and myocardial contractile force (MCF) in a dog.

more sustained rise. The increase in myocardial contractile force occurred one minute after the i.v. injection of $PGF_{2\alpha}$ and coincides with the second rise in cardiac output. $PGF_{2\alpha}$ decreased mean left atrial pressure by 2 mm Hg, whereas heart rate and mean right atrial pressure remained essentially unchanged. As illustrated in Fig. 1, the magnitude of the increases in pulmonary arterial pressure and in myocardial contractile force produced by PGE_1 or PGA_1 was significantly smaller and greater, respectively than that by $PGF_{2\alpha}$.

Discussion. From the present study, it is evident that PGE_1, PGA_1, and $PGF_{2\alpha}$ increase pulmonary arterial pressure, myocardial contractile force, and cardiac output, and decrease mean left atrial pressure. Both PGE_1 and PGA_1 decrease systemic arterial pressure, whereas $PGF_{2\alpha}$ increases it. The hemodynamic changes induced by PGE_1 are qualitatively similar to those induced by

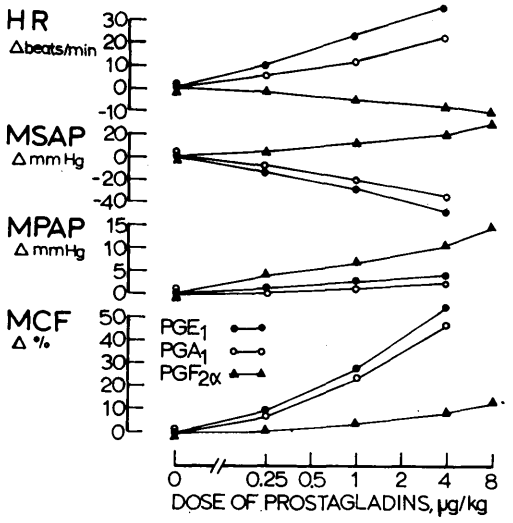

FIG. 2. Effects of the i.v. administration or graded doses (0.25–8 μg/kg) of PGE_1, PGA_1 and $PGF_{2\alpha}$ on heart rate (HR), mean systemic arterial pressure (MSAP), mean pulmonary arterial pressure (MPAP), and myocardial contractile force (MCF) in 21 dogs. (●,○,▲) represent average effects of the different parameters in 7 dogs.

PGA_1, but their magnitude is slightly greater than the latter. On the other hand, the magnitude of the increases in cardiac output and in myocardial contractile force induced by $PGF_{2\alpha}$ is slightly smaller than that by either PGE_1 or PGA_1. However, the increment in pulmonary arterial pressure induced by $PGF_{2\alpha}$ is significantly greater than that by PGE_1 or PGA_1.

The hypotensive effect of PGE_1 and PGA_1 is most likely due to the marked vasodilatation of the peripheral vasculature, i.e., the decreased total peripheral resistance, since both PGE_1 and PGA_1 enhance myocardial contractility and cardiac output (6). The increased myocardial contractility by PGE_1 and PGA_1 is caused by the direct positive inotropic action on the myocardium, since this effect is not modified by the administration of propranolol (6). Obviously, the augmented sympathoadrenal activity reflexly elicited by the hypotensive effect of PGE_1 and PGA_1 would partially play a role on the increased myocardial contractility (14). As a consequence, left atrial pressure usually decreases. PGE_1 and PGA_1 increase transiently, pulmonary arterial pressure by the temporary increase in systemic venous return (15). It has been found in this laboratory that the repeated administration of larger doses (4 μg/kg or more) frequently caused a greater hypotension and no change or slight decreases in myocardial contractile force and in cardiac output. The marked hypotension could well decrease coronary blood flow, thereby reducing myocardial contractile force (16).

The hypertensive effect of $PGF_{2\alpha}$ is due mainly to its vasoconstrictor action and the increased cardiac output. DuCharme and Weeks (5) found that $PGF_{2\alpha}$ increases cardiac output by the increase in systemic venous return. They ascribed the augmented systemic venous return to the primary venoconstrictor action of $PGF_{2\alpha}$. In the present study, $PGF_{2\alpha}$ causes multiphasic changes in cardiac output, whereas the changes in systemic arterial pressure and myocardial contractile force are practically monophasic. The initial, transient rise in cardiac output is followed by the subsequent decrease as mean pulmonary arterial pressure increases significantly. Thereafter, pulmonary arterial pressure deceases and myocardial contractile force increases together with the gradual, more sustained increases in cardiac output and systemic arterial pressure and with the decrease in mean left atrial pressure. The delayed increase in myocardial contractile force could be explained by the simple summation of two hemodynamic factors, i.e., (a) the coronary arterial constrictor action, and (b) the positive inotropic action of $PGF_{2\alpha}$. It was found that the decrease in coronary arterial blood flow per se reduces myocardial contractile force (16). Likewise, the hypertensive effect of $PGF_{2\alpha}$ is followed by the changes in myocardial contractility and cardiac output. Further studies are indicated to elucidate these phasic hemodynamic changes induced by $PGF_{2\alpha}$.

Summary. The cardiovascular effects of PGE_1, PGA_1, and $PGF_{2\alpha}$ were studied in anesthetized, open chest dogs. It was found that PGE_1, PGA_1, and $PGF_{2\alpha}$ decrease left atrial pressures, and increase heart rate, pulmonary arterial pressure, cardiac output, and myocontractile force. However, both PGE_1 and PGA_1 are vaso-dilators and decrease

systemic arterial pressure. The multiple hemodynamic changes induced by the three prostaglandins are caused, not only by their direct effect on the peripheral vasculatures, but also by their effects on the myocardium.

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Regulation of Cell Lipid Metabolism and Accumulation. VII. Increase by Glycerol of the Polar Lipid and Triglyceride Content of Cultured Cells* (32938)

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The discovery of Polge *et al.* (1) that spermatozoa are preserved by freezing in 5% glycerol was extended to cultured mammalian cells in 1954 by Scherer and Hoogasian (2). They found that mouse fibroblast (L) and HeLa cells suspended in a glycerol–serum solution remained viable for months when frozen either rapidly or slowly and stored at −70°C. Subsequently, Stulberg, *et al.* (3) reported that human fibroblast cells were killed by rapid freezing but survived when the temperature was reduced in a programmed apparatus at 1°C per min.

Several years ago we noticed the presence of perinuclear particles in the cytoplasm of cultured mammalian cells that have been subjected to either the rapid or slow freezing procedure in glycerol (3). Although the particles can be detected in suspended cells immediately after thawing, they are more conspicuous after the cells have attached and spread out on a glass surface. In living cells viewed under the phase contrast microscope, the particles appear as dark bodies ranging from 0.3 to 1.0 μ in diameter. In fixed cells, the particles stain brilliantly with lipid soluble dyes such as oil red O.

The formation of these lipophilic particles is unrelated to the time of cell storage at −80° C, and they disappear after several cell divisions in glycerol-free medium. This latter observation led us to test the effect of glycerol on unfrozen cells and it was found that the addition of glycerol to a medium containing horse serum caused the formation of lipophilic particles in less than 24 hours. Furthermore, incorporation of the higher and lower homologues of glycerol in the medium had a

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