Effects of Prostaglandins E_1 and $F_{2\alpha}$ on the Peripheral Circulation in the Cat[1] (37027)

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It has been widely accepted that the overall cardiovascular effect of prostaglandin E_1 (PGE_1), in most common experimental animals, is depressor in nature (1). In contrast, $PGF_{2\alpha}$ is also a potent depressor agent in the cat and rabbit (2, 3) but produces a moderate pressor response in rats and dogs (4, 5). The hemodynamic factors responsible for the depressor response to $PGF_{2\alpha}$ in cats and rabbits have not been adequately clarified (6). The present study was undertaken to investigate the direct effect of PGE_1 and $PGF_{2\alpha}$ on the peripheral vasculature in the isolated perfused hindlimb preparation of the cat. An attempt was made to determine to what extent direct vasodilation may be responsible for the overall decrease in systemic arterial pressure.

Methods. Twelve adult cats of either sex, weighing 2.5–4 kg were anesthetized with pentobarbital (36 mg/kg ip). The right subclavian artery and vein were cannulated for measuring systemic arterial pressure and iv injection of drugs. The abdominal aorta was cannulated both distally and proximally and the hindlimbs were perfused at a constant rate by means of a Sigmamotor pump (Fig. 1). Systemic arterial and perfusion pressures were continuously recorded with a Statham pressure transducer (P23Db) and heart rate by means of a Grass tachograph (7P4D). PGE_1 and $PGF_{2\alpha}$ were dissolved in 20 μl of 95% ethanol and further diluted to 10–100 μg/ml solutions before ia or iv injection. In several preparations hexamethonium chloride (2–3 mg/kg) was given in order to eliminate reflex effects.

Results. The response to ia injections of 0.1–0.3 μg/kg PGE_1 was a consistent and extensive reduction in perfusion pressure, which is indicative of vasodilation of the perfused vasculature. This vasodilator response persisted for periods of 10–15 min before returning to control levels (Fig. 2A). The recovery time and extent of the direct vasodilator effect of PGE_1 corresponds closely with that seen following iv injections of 4–8 μg/kg PGE_1. In contrast, the responses to ia $PGF_{2\alpha}$ were not consistent. Although the response was always depressor in nature, there was considerable variability between preparations in the dose necessary to produce even the most minimal vasodilation. In three animals as little $PGF_{2\alpha}$ as 0.1–0.2 μg/kg ia was sufficient to demonstrate a marked lowering of the perfusion pressure (Fig. 2B), while in the other nine as much as 2–5 μg/kg was required. In addition, the responses to $PGF_{2\alpha}$ recovered fully within 2–5 min regardless of

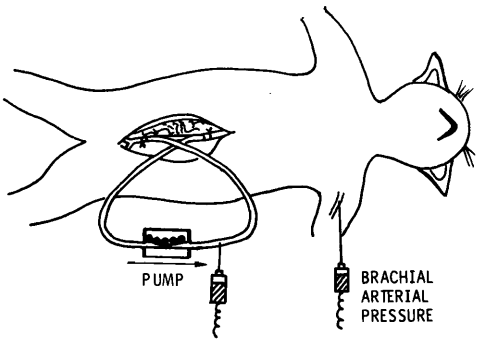

Fig. 1. Schematic representation of the perfused hindlimb preparation in the cat. Constant blood flow maintained by means of Sigmamotor pump and change in vascular resistance recorded as a change in pressure of perfused region. Systemic blood pressure and heart rate recorded from brachial artery.

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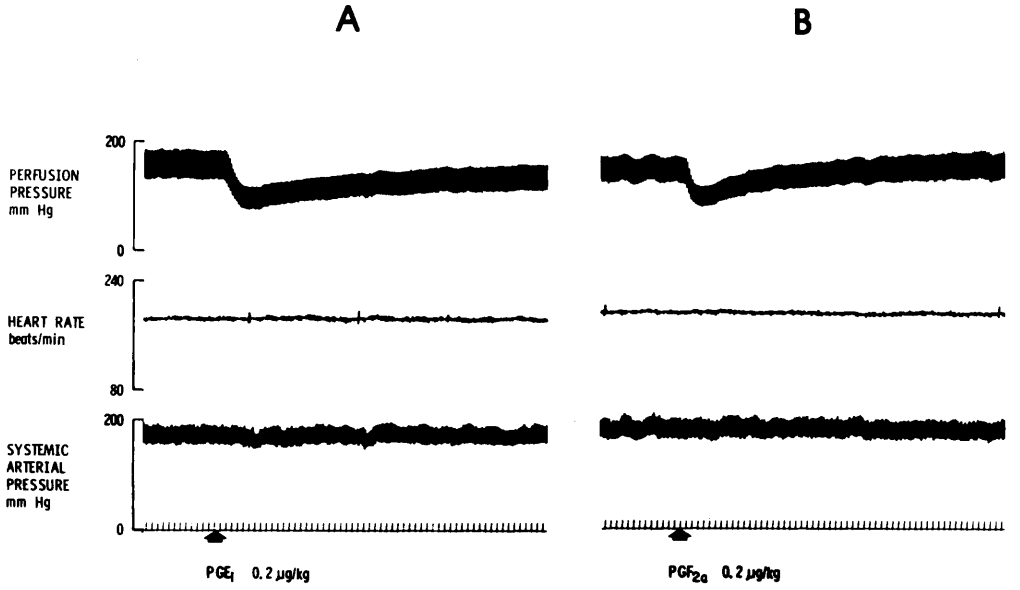

FIG. 2. Effects of ia administration of a single dose (0.2 μg/kg) of PGE$_1$ (A); and (0.2 μg/kg) of PGF$_{2\alpha}$ (B) in the same cat. Time mark indicates 5 sec intervals.

the dose given. This short time course for PGF$_{2\alpha}$ ia does not correspond with the prolonged recovery period usually seen after an iv injection of this substance as shown in Fig. 3. The delayed and prolonged bradycardia shown in Fig. 3 is characteristic of iv PGF$_{2\alpha}$ and is most likely reflex in nature, as it is abolished by vagotomy. The problem of tachyphylaxis to PGF$_{2\alpha}$ upon repeated administration was also considered. In these preparations, hexamethonium was previously administered in order to block reflex and tonic nervous influences. As shown in Fig. 4, after ganglionic blockade, there was little if any reduction in the response to repeated graded ia doses of PGF$_{2\alpha}$.

Discussion. The present results support the concept that PGE$_1$ exerts its depressor effect mainly by reducing total peripheral resistance through its potent vasodilator action. These observations on the perfused hindlimb preparation are consistent with the overall cardiovascular effect of PGE$_1$ in the cat and with other species as well (1, 6).

Horton and Main (2) and Änggard and Bergström (3) have shown indirectly that PGF$_{2\alpha}$ increased blood flow in skeletal muscle. However, due to the early scarcity of PGF$_{2\alpha}$, the number of experiments they were able to perform was too small to enable them to determine the relative contribution of this component to the overall cardiovascular response. The great variability from one animal to another and the transient nature of the response

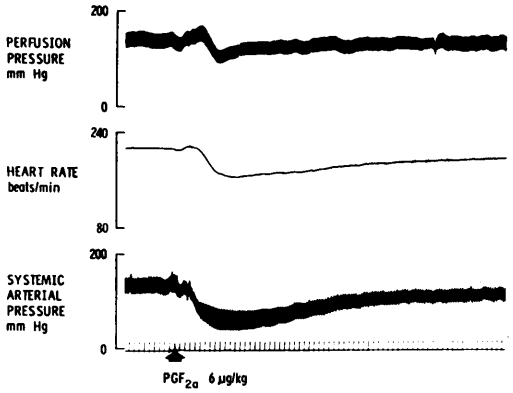

FIG. 3. Effects of iv administration of a single dose (6 μg/kg) of PGF$_{2\alpha}$. Response of perfusion pressure delayed 25 sec due to transit time through pump mechanism. Note that decrease in perfusion pressure is fully recovered (within 4 min) while heart rate and systemic pressure remain depressed. In this case, the systemic arterial pressure returned to the control level 22 min after the injection.

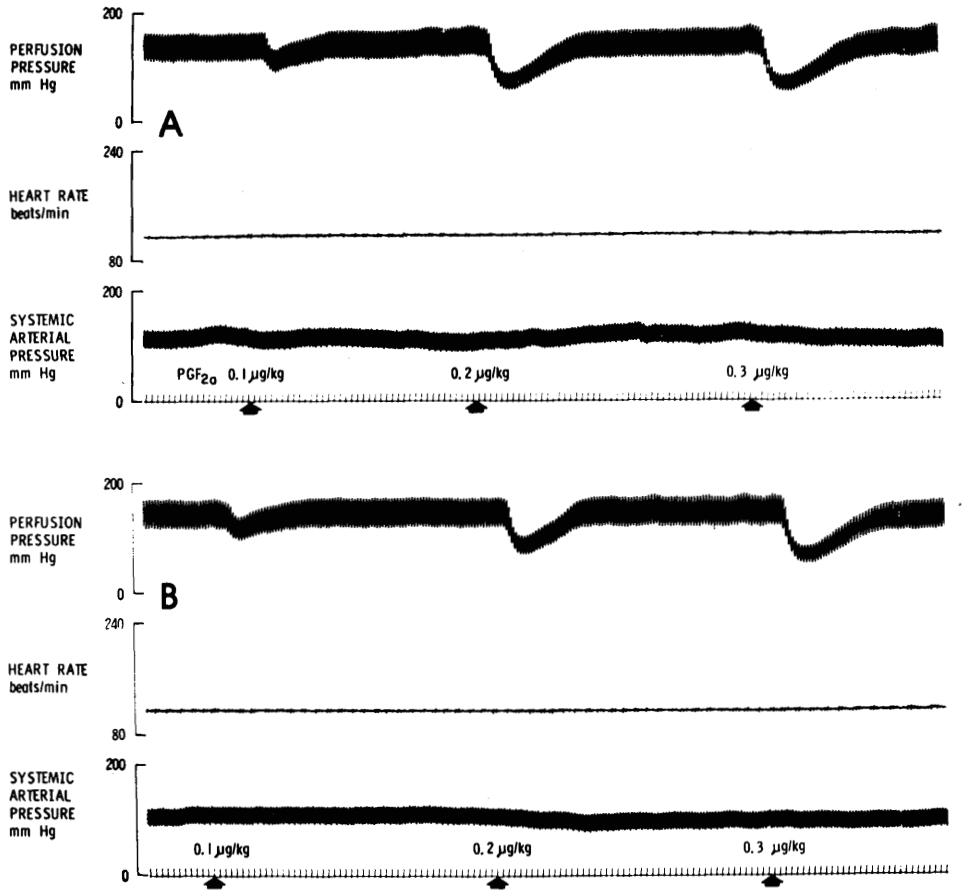

FIG. 4. Effects of repeated graded ia doses of PGF$_{2\alpha}$ after ganglionic blockade. Panels A and B are continuous record. Note lack of tachyphylaxis to PGF$_{2\alpha}$ in this preparation.

suggests that direct vasodilation plays a relatively minor role in the overall cardiovascular response to PGF$_{2\alpha}$. It is probable that the delayed long lasting bradycardia contributes to the prolongation of the depressor effect. In addition, Änggard and Bergström (3) reported that iv PGF$_{2\alpha}$ increased right ventricular pressure. We have observed that by this route of administration, PGF$_{2\alpha}$ but not PGE$_1$ increased pulmonary arterial pressure by as much as 40 mm Hg after 4–8 μg/kg (7). It is likely that the reduced cardiac output due to this constriction of the pulmonary vasculature contributes in large measure to the overall cardiovascular effect of PGF$_{2\alpha}$.

These observations become especially relevant when one considers several agents that have recently been suggested to be selective blockers of the vasodepressor action of PGF$_{2\alpha}$. Levy and Lindner (8) reported that in the rabbit meclofenamic acid selectively blocked proposed vascular smooth muscle receptors sensitive to PGF$_{2\alpha}$. Villanueva *et al.* (9) observed that polyphloretin phosphate (PPP) antagonized the action of PGF$_{2\alpha}$ but not PGE$_1$ on the systemic arterial pressure in the cat. This effect of PPP in blocking the PGF$_{2\alpha}$ lowering of blood pressure in the cat has also been reported by Mathé *et al.* (10). It is likely that these agents are demonstrating their selectivity not by acting upon the vascular smooth muscle but upon hemodynamic factors unique to PGF$_{2\alpha}$ which may contribute in even larger part to the overall cardiovascular response.

Summary. Ia administration of both PGE$_1$ and PGF$_{2\alpha}$ result in a decrease of the perfusion pressure in the isolated hindlimb prepa-

ration in the cat. This vasodilator action of PGE$_1$ corresponds well with and appears sufficient to account for the overall cardiovascular response to this agent. On the other hand, ia PGF$_{2\alpha}$ produces a variable and transient response in this isolated preparation. Direct vasodilation does not appear to be the only hemodynamic mechanism responsible for the overall depressor action of iv PGF$_{2\alpha}$. It was observed that there is little, if any, tachyphylaxis to the direct vasodilator actions of PGF$_{2\alpha}$.

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