Anaesthesia was induced with thiopentone (30–40 mg/kg i.v.) and maintained with chloralose (25–35 mg/kg i.v.) and pentobarbitone (7.5–10.5 mg/kg i.v.). The dogs were artificially ventilated; arterial pO_2 was maintained above 90 mm Hg and pCO_2 in the range 25–40 mm Hg. A loading dose of creatinine (50 mg/kg in 0.9% w/v saline i.v.) was followed by a maintenance infusion (0.42 $mg/kg^{-1}min^{-1}$ in 0.9% saline at 0.25 $ml/kg^{-1}min^{-1}$) via a cannulated femoral vein. Arterial (BP) and venous (VP) blood pressures were measured from brachial vessels with pressure transducers connected to a chart recorder. Heart rate (HR) was recorded by integrating the arterial pulse. An electromagnetic flow probe (2–4 mm diameter) was fitted to the left renal artery to measure renal blood flow (RBF). The ureters were cannulated and urine flow (UV) from the left kidney recorded by integrating the signal from a photo-electric drop counter.

Renal arterial (i.a.) infusions of PGI_2 (30–300 ng/min for 15–30 min in 5 dogs) caused dose dependent increases in RBF, UV and sodium excretion ($U_{Na}V$), $U_{Cl}V$, $U_{Osm}V$, and reductions in calculated renal vascular resistance (RVR) and filtration fraction (FF) without altering BP or HR. Qualitatively similar responses to PGI_2 (1000–3000 ng/min i.a.) were associated with hypotension and tachycardia. VP and creatinine clearance (C_{Cr}) were unaffected.

Intravenous infusion of PGI_2 (30–300 ng/min in 3 dogs) tended to increase RBF but reduced $U_{Na}V$, $U_{Cl}V$, $U_{Osm}V$, while BP, HR, C_{Cr}, FF, UV and U_KV were unaltered. Larger doses (1000–3000 ng/min i.v.) caused pronounced hypotension accompanied by further elevations of RBF and HR, but reductions in all other variables. The stable metabolite of prostacyclin, 6-oxo-$PGF_{1\alpha}$ (10,000 ng/min) had no effect by either i.v. or i.a. routes.

After meclofenamate (2.5 mg/kg i.v. in 2 dogs), RBF was unchanged, though the increase in RBF to PGI_2 (300 ng/min i.a.) was enhanced.

As glomerular filtration rate (C_{Cr}) was unaltered by sub-hypotensive doses (i.a.) of PGI_2, the reduction in calculated FF could be explained by efferent arteriolar dilatation (Bolger, Eisner, Ramwell & Slotkoff, 1976). Similarly, the increased $U_{Na}V$ and $U_{Cl}V$ resulted from reductions in tubular Na^+ and Cl^- reabsorption, rather than through increases in their filtered loads. Endogenous PGI_2 synthesized by kidney vessels may influence renal function.

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Disappearance of prostacyclin (PGI_2) in the circulation of the dog

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Prostacyclin (PGI_2) is a potent endogenous vasodilator in dogs (Armstrong, Chapple, Dusting, Hughes, Moncada & Vane, 1977a; Dusting, Moncada & Vane, 1977) rats and rabbits (Armstrong, Lattimer, Moncada & Vane, 1977b). Prostaglandin E_2 (PGE_2) is less potent as a hypotensive agent when given intravenously rather than intra-arterially because of extensive pulmonary metabolism (Ferreira & Vane, 1967), but prostacyclin is of similar potency when given by either route (Armstrong *et al.*, 1977a, b). We have now examined the stability of prostacyclin in blood, and its removal by various vascular beds of the dog.

Prostacyclin was detected by direct bioassay in blood continuously withdrawn from the arterial circulation of chloralose anaesthetized dogs (Vane, 1964). The vascular bioassay tissues (spiral strips of rabbit coeliac artery, RbCA; bovine coronary artery, BCA) were relaxed by prostacyclin (threshold 2–5 ng/ml), whereas gastro-intestinal bioassay tissues (rat stomach strip, RSS; rat colon, RC) were contracted by prostacyclin (threshold above 10 ng/ml). All bioassay tissues were insensitive to 6-oxo-$PGF_{1\alpha}$ (up to 100 ng/ml).

To measure the stability of prostacyclin in blood, a coil of silicone tubing was interposed between the blood supply and the bioassay tissues such that a transit time of up to 5 min could be achieved. Prostacyclin infusions (20–80 ng/ml) were made at different points in the coil and their effect compared with infusions of prostacyclin close to the assay tissues. From the disappearance of the activity on RbCA, BCA or RSS the half-life in blood was calculated to be 3.1 ± 0.4 min (6 experiments). This probably reflects chemical rather than enzymic breakdown for the half-life of prostacyclin in buffer at 37°C and pH 7.5 is about 3 minutes.

To study survival through the lungs, prostacyclin was infused alternately through two catheters whose tips were located in the right atrium and in the ascending aorta or left ventricle. Intraaortic or intravenous infusions of prostacyclin (0.1–0.5 μg kg^{-1}-min^{-1}) for 10–15 min induced similar hypotensive effects and similar steady-state relaxations of the BCA. In the same dogs more than 90% of PGE_2 (0.05–0.5 μg $kg^{-1}min^{-1}$), assayed by contraction of RSS, was removed through the lungs.

The disappearance of prostacyclin in the hindquarters and liver was studied by infusions (0.2–1.0 μg $kg^{-1}min^{-1}$) through catheters inserted into the abdominal aorta (just above the iliac bifurcation) and the portal vein respectively. By comparing relaxation of BCA during infusion into the right atrium with infusions through these catheters it was estimated that the hind quarters removed 48 ± 4% (4 dogs) of prostacyclin in one passage and the liver removed 73% and 75% (2 dogs).

Thus, in contrast to PGE_2 and $PGF_{2\alpha}$ the activity of prostacyclin does not disappear after passage through the lungs. However, prostacyclin is inactivated to about the same extent as PGE_2 and $PGF_{2\alpha}$ in the hind quarters and the liver (Ferreira & Vane, 1967).

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Enzyme in rabbit kidney converts prostaglandin $F_{2\alpha}$ directly to prostaglandin E_2 *in vitro*

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Classical prostaglandins (PG) such as PGE_2 and $PGF_{2\alpha}$ are metabolised in most tissues by the sequential action of prostaglandin 15-hydroxydehydrogenase and prostaglandin Δ–13 reductase, yielding biologically inactive 13,14-dihydro-15-keto prostaglandins. We have recently demonstrated such pathways of $PGF_{2\alpha}$ breakdown in the kidneys of several species and observed in rabbit kidney a novel enzyme which converts $PGF_{2\alpha}$ directly to PGE_2 (Hoult & Moore, 1977).

Highspeed (100,000 *g*) supernatants obtained from homogenized kidneys of adult male animals were incubated at 37°C with 5 mM NAD^+ and PGE_2 or $PGF_{2\alpha}$ (10 μg/ml) containing 0.05 μCi [$^3H_7$]-PGE_2 or [$^3H_1$-9β]-$PGF_{2\alpha}$. Samples removed at timed intervals were either assayed directly on up to four rat fundus strips, or acidified, extracted and evaporated prior to scintillation counting and either bioassay or thin layer radiochromatography in solvent F6 (Andersen, 1969).

Guinea pig, rat and rabbit kidneys (in descending order of activity) metabolised PGE_2 exponentially and more rapidly than $PGF_{2\alpha}$: $T_{\frac{1}{2}}$ measured by bioassay were 3.0 ± 0.3, 15.5 ± 1.4, 49.8 ± 3.9 min for PGE_2, and 7.9 ± 0.9, 36.6 ± 2.8, 132.0 ± 4.5 min for $PGF_{2\alpha}$ (n = 6). The bioassay and radio-t.l.c. results agreed closely except for $PGF_{2\alpha}$ metabolism by rabbit kidney; in 8 experiments the biological activity of the incubation increased to 207.9 ± 16.6%, peaking at 10–20 min, and thereafter declined as the active material was itself metabolised. Simultaneous radiochemical experiments showed a progressive loss of the 9β-tritium label consistent with oxidation of the secondary alcohol at C-9 to a ketone. Generation of biologically active material was prevented reversibly at 4°C and inhibited irreversibly by preincubation for 15 min at 50°C or 1 min at 100°C. Thin layer chromatography in five solvents of material derived from large scale incubations extracted at the peak of biological activity showed that >80% of the bioassayable material recovered was located in the 'PGE_2 zone'. It possessed properties similar to PGE_2 in several biological assays, and could be converted to $PGF_{2\alpha}$ by sodium borohydride reduction.

This enzyme is located exclusively in the rabbit kidney cortex: using a radiochemical method and highspeed supernatants containing approximately equal amounts of soluble protein, 68.9 ± 2.3% $PGF_{2\alpha}$ was converted to E-type derivatives in 240 min by cortex, but only 8.2 ± 1.8% by medulla (n = 5). Conversion of $PGF_{2\alpha}$ to PGE_2 was observed biologically at a wide range of substrate concentrations (100 μg/ml down to 0.5 μg/ml). There was no evidence from either bioassay or radiochemical methods for conversion of $PGF_{2\beta}$ (10 μg/ml) to PGE_2