Cardiovascular Pharmacology of Prostaglandin B_1 and B_2 in the Intact Dog[1] (37458)

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Prostaglandins E_1 and E_2 (PGE_1, PGE_2) are synthesized from their fatty acid precursors, dihomo-8-linolenic acid and arachidonic acids, respectively (1–4). Current evidence suggests that PGE compounds may be dehydrated to form the corresponding prostaglandin A (PGA) compounds which are potent vasodilator substances (5–7) and are believed to be converted by a plasma enzyme, prostaglandin isomerase, to the more potent vasodilator compounds known as prostaglandins C (PGC) (5–7). Prostaglandins B_1 and B_2 (PGB_1, PGB_2) are believed to be the inactive products of PGA metabolism (1–7).

In vitro, PGB_2 is a potent constrictor of isolated canine cutaneous and mesenteric arterial and venous smooth muscle (8, 9) and rat pancreatic arteries (10–12). Superfusion of mesenteric and cutaneous vessels with the same concentration of PGB_2 (2.8×10^{-8} *M*) resulted in constriction of cutaneous vessels approximately three times greater in magnitude than that observed in the mesenteric vasculature (8, 9). PGB_2 increases ^{45}Ca efflux but inhibits ^{22}Na efflux and ^{40}K uptake in concentrations which constrict vascular smooth muscle *in vitro* (9). However, PGB compounds are considered to possess very weak depressor activity *in vivo* in the rat [Weeks, J. R., personal communication (11)].

Since PGB_2 is a potent vasoconstrictor *in vitro,* the relative absence of cardiovascular activity of this prostaglandin *in vivo* could result from the further *in vivo* metabolic inactivation of PGB_2. Alternatively, PGB_2 may constrict some vascular beds and dilate others. When systemic arterial pressure (SAP) is used as the sole indicator of prostaglandin activity the resultant hemodynamic response to PGB_2 could be small or nonexistent.

The following experiments were designed to evaluate the spectrum of cardiovascular activity of PGB_1 and PGB_2 in pharmacologically intact pentobarbital anesthetized dogs. The results demonstrate that the PGB's have a spectrum of activity on the cardiovascular system which differs from prostaglandins of the E, F and A series.

Methods and Materials. Mongrel dogs of either sex (12–14 kg), were anesthetized with sodium pentobarbital (35 mg/kg, iv). Positive pressure artificial respiration was applied throughout the experiment with a Harvard respirator. Both external jugular veins were cannulated and Swan-Ganz catheters inserted into the right atrium, right ventricle and pulmonary artery. The positions of the catheters were verified on postmortem examination of the animal at the conclusion of each experiment. A cannula was inserted into the left ventricle via a carotid artery for measurement of left ventricular pressure (LVP). The contralateral carotid artery was utilized for measurement of (SAP). Heart rate (HR) was measured electronically with a cardiotachometer triggered by the arterial pressure pulse. HR, SAP, LVP, pulmonary artery pressure (PAP), right ventricular pressure (RVP), and right atrial pressure (RAP) were measured with Statham arterial and venous transducers and recorded

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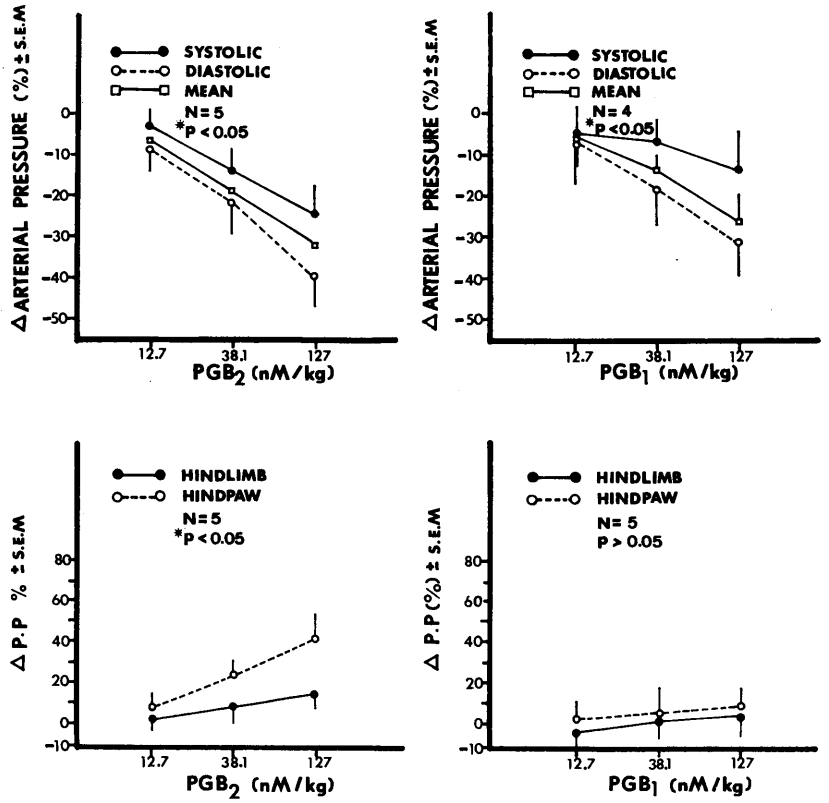

FIG. 1. Effect of iv administration of PGB_1 and PGB_2 on systemic arterial pressure and perfusion pressure in the canine hindlimb and hindpaw. The ordinate represents the change in pressure (expressed as a percentage of base line pressure ± the standard error of the mean) at the peak of the response to iv administration of PGB_1 and PGB_2 (4.5 to 45 μg/kg). The abscissa represents the quantity of PGB injected expressed as nanomoles per kilogram. The *N* value denotes the number of animals used in calculation of the mean. * The existence of a significant regression for the parameter under study after administration of PGB. The control pressures prior to administration of prostaglandins B were (mm Hg ± SE): systolic (164 ± 15); diastolic (104 ± 18); mean (121 ± 13); hindlimb (128 ± 10); and hindpaw (121 ± 13).

on a Beckman type RM 8-channel recorder.

Sodium heparin (1000 units/kg) was administered to each animal through a cannula inserted into the dorsal-metatarsal branch of the saphenous vein. The contralateral cranial-tibial artery and hindlimb were simultaneously perfused by means of two Harvard peristaltic pumps with autologous blood taken from a common iliac artery. Flow in the hindpaw averaged 22.7 ± 1.7 (SEM) ml/min, while that in the hindlimb averaged 62.9 ± 2.7 ml/min. Isolation of the hindlimb and hindpaw was confirmed by turning off the pumps and observing the residual pressure which approached small vein pressure (13). Since flow in the hindlimb and hindpaw was maintained constant, changes in hindlimb (HLPP) and hindpaw perfusion pressures (HPPP) were equivalent to changes in vascular resistances.

Partial dose–response curves were obtained to the iv administration of PGB_1 (12.7 to 127 nmoles/kg) and PGB_2 (12.7 to 127 nmoles/kg). Agonists were dissolved in 95% ethanol and diluted with saline immediately prior to experimentation. PGB_1 and PGB_2 were administered in randomized fashion to each animal. Intravenous administration of 0.01% ethanol, in equivalent volumes used for injection of prostaglandins, produced no

cardiovascular effects. In a separate group of experiments PGB_2 (0.038 to 38 nmoles) was administered, as a bolus, directly into the perfusion circuit prior to its entrance into the tibial artery.

Statistical analyses. Data were analyzed with Student's paired t test (14) and linear regression analyses (14). The change in each hemodynamic parameter after administration of PGB_1 was compared to that change observed after PGB_2 with Student's paired t test (14). A p value equal to or less than 0.05 was chosen for statistical significance.

Results. The results of the intravenous (iv) administration of PGB_2 and PGB_1 on systemic arterial pressure and hindlimb and hindpaw vascular resistances are summarized in Fig. 1. PGB_2 produced dose-dependent decreases ($p < 0.05$) in systemic systolic, diastolic, and mean arterial pressures. In contrast to these findings, perfusion pressures in the hindpaw and hindlimb were significantly increased from control values. PGB_2 was a more potent constrictor of the hindpaw than of the hindlimb ($p < 0.05$). PGB_1 produced effects on SAP similar to PGB_2 (Fig. 1). However, PGB_1 was less potent a vasodilator ($p < 0.05$) than PGB_2. PGB_1 did not produce significant increases in either HLPP or HPPP.

In order to determine if PGB_2-induced increases in HPPP were a direct action of this prostaglandin on the cutaneous vasculature, or mediated by reflex mechanisms in response to the decrease in systemic pressure, this prostaglandin was injected directly into the perfusion circuit prior to its entrance into the tibial artery. The results are summarized in Fig. 2. Intra-arterial (ia) administration of graded doses of PGB_2 produced dose-dependent increases in perfusion pressure. The rise in perfusion pressure was rapid in onset. However, the response declined slowly.

The effect of prostaglandin B on PAP and ventricular function are summarized in Fig. 3. PGB_2 produced dose-dependent increases in both pulmonary systolic and diastolic arterial pressures. The percentage change in PDP was significantly greater than the change in PSP. In contrast PGB_1 produced less enhancement ($p < 0.05$) of PSP and

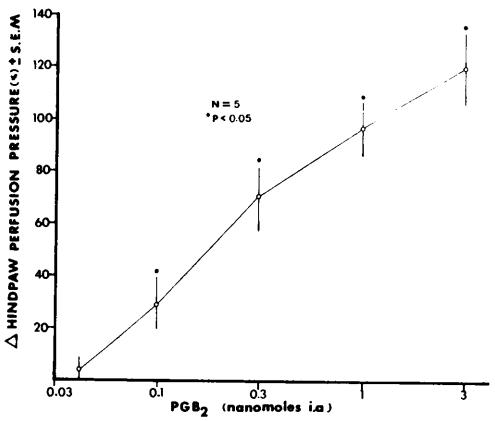

FIG. 2. Effect of intra-arterial administration of PGB_2 on perfusion pressure of the canine hindpaw perfused at constant flow. The ordinate represents the change in perfusion pressure expressed as percentage of control perfusion pressure (123 ± 7 mm Hg). The abscissa represents the dose of PGB_2 (0.45 to 45 μg) expressed as nanomoles. * The change in perfusion pressure was significantly different from control perfusion pressure.

PDP than PGB_2. Furthermore, no significant differences existed in the magnitude of PGB_1-induced increases in PSP when compared with PDP.

RVP and LVP were affected differently by PGB_1 and PGB_2 (Fig. 3). PGB_2 produced dose-dependent increases in RVP and decreased LVP. PGB_2-induced depression of LVP was maximal after administration of 38.1 nmoles/kg. PGB_1 (lower doses) decreased RVP, whereas the high dose increased RVP. PGB_1 produced dose-dependent decreases in LVP. PGB_1 was a more potent depressant ($p < 0.05$) of LVP than PGB_2 (Fig. 3).

The changes in heart rate after PGB_1 and PGB_2 are shown in the top of Fig. 4. Both prostaglandins decreased the HR of the pentobarbital-anesthetized dog. PGB_1 was less potent ($p < 0.05$) than PGB_2. The change in HR after administration of PGB_1 was only significant with the high dose of this prostaglandin. RAP (Fig. 4) and left ventricular end diastolic pressure (LVEDP) were unchanged after iv administration of PGB_1 and PGB_2. LVEDP was 6 ± 2 and 6 ± 3 mm Hg before and after ($p > 0.05$), respec-

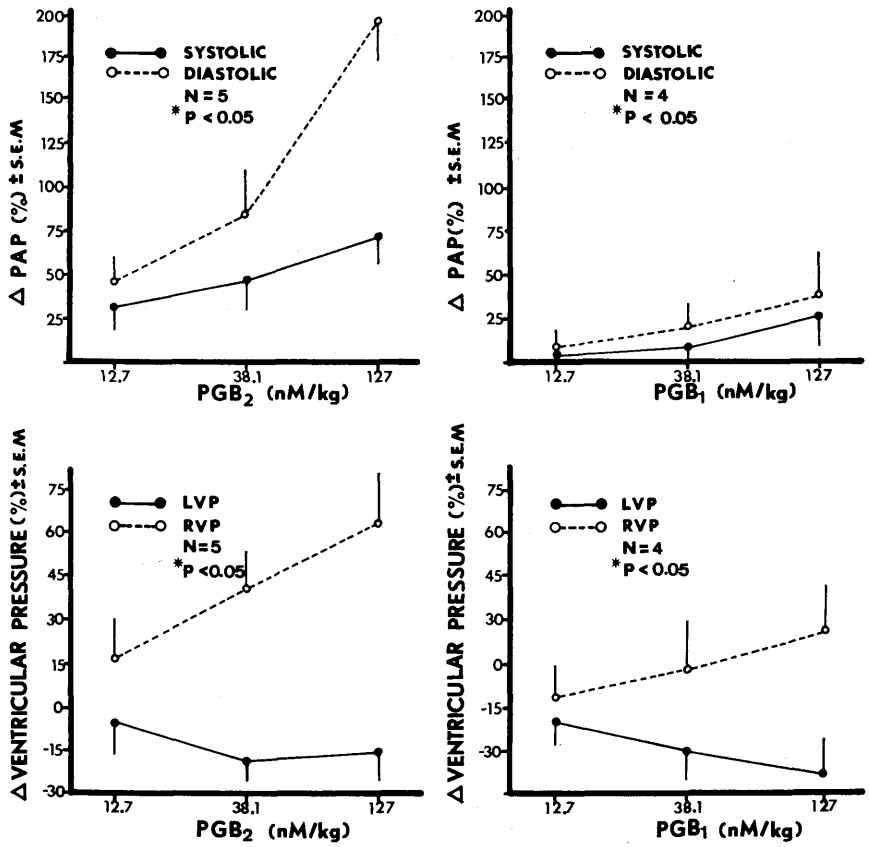

FIG. 3. Effect of iv administration of PGB_1 and PGB_2 on canine pulmonary artery and ventricular pressures. The ordinate represents the change in pressure (expressed as a percentage of baseline pressure ± the standard error of the mean) at the peak of the response to iv administration of PGB_1 and PGB_2 (4.5 to 45 μg/kg). The abscissa represents the quantity of PGB injected expressed as nanomoles per kilogram. The *N* value denotes the number of animals used in the calculation of the mean. * Each of the mean changes differed significantly from base line pressure and the existence of a significant regression. RVP = right ventricular pressure; LVP = left ventricular pressure. The change in LVP observed after 127 nmoles/kg PGB_2 was not significantly different ($p > 0.05$) from Δ LVP to 38.1 nmoles/kg PGB_2. Before PGB control mean pressures were (mm Hg ± SEM): pulmonary systolic arterial (26.8 ± 2.1); pulmonary diastolic arterial (13.2 ± 1.7); LVP (168 ± 12); and RVP (27.2 ± 2.9).

tively, PGB_1 (45 μg/kg; 127 nmoles/kg). LVEDP was 4 ± 2 and 4 ± 3 mm Hg before and after ($p > 0.05$), respectively, PGB_2 (45 μg/kg).

Discussion. From the present study it is evident that PGB_1 and PGB_2 are not inactive metabolites of their precursors PGA_1 and PGA_2. PGB compounds increase PAP and RVP without any significant effect on LVEDP. This finding is consistent with a direct vasoconstrictor action of prostaglandins on the pulmonary vascular smooth muscle (15–17). Similar findings have been observed in the isolated perfused lobe of canine lung (Kadowitz, P. J., personal communication). PGB_2, and to a lesser extent PGB_1, constrict the canine hindpaw perfused at constant flow (Figs. 1 and 2). These findings are in contrast to the hemodynamic changes produced by the parent compound PGA_1 and PGA_2. PGA compounds dilate the cutaneous vascular bed and increase pulmonary pressure by

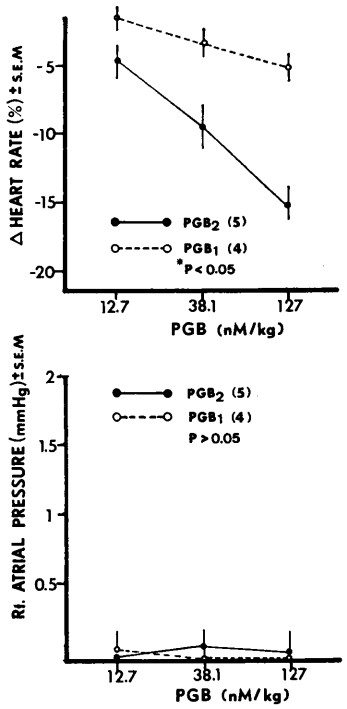

FIG. 4. Effect of iv administration of PGB_1 and PGB_2 on canine heart rate (HR) and right atrial pressure (RAP). The ordinate represents the change in HR (expressed as a percentage of resting HR) and the change in RAP (expressed as mm Hg ± the standard error of the mean) after iv administration of PGB_1 and PGB_2 (4.5 to 45 μg/kg). The abscissa represents the quantity of PGB injected expressed as nanomoles per kilogram. The number of parentheses denotes the number of animals used in calculation of the mean. * The decrease in HR after each dose of PGB was significantly different from control. PGB's had no effect on RAP. Control mean RAP was 7 ± 3 mm Hg while control heart rate was 147 ± 15 BPM.

increasing flow and venous return (18–23). PGA_1 and PGE_1 decrease arterial pressure, LAP, HLPP and HPPP, but increase myocardial contractile force and heart rate (18–23). PGB compounds, however, decrease SAP but increase HPPP and HLPP, and decrease LVP and HR. Therefore, the effects of PGB compounds on cardiovascular hemodynamics differ from those of the other known prostaglandins.

Some tentative conclusions may be drawn from this study concerning the action of PGB compounds. Hypotension, as a result of vasodilatation, would activate reflex sympathoadrenal discharge resulting in an increase in LVP and HR. The opposite effect is observed after PGB compounds. Therefore, prostaglandin B_1 and B_2 may exert a direct depressant effect on the myocardial cells. It is unlikely that pentobarbital anesthesia, which possesses vagolytic activity (24) could account for the decrease in heart rate produced by PGB compounds. Reflex tachycardia to vasodilator stimuli occurs in pentobarbital-anesthetized dogs (13). In experiments performed under similar conditions nitroglycerin consistently elicited reflexly mediated increases in heart rate. Furthermore, neurally mediated bradycardia elicited by digoxin-induced release of acetylcholine is abolished after pentobarbital anesthesia (25). Therefore, it is unlikely that pentobarbital anesthesia, as a result of the somewhat higher initial heart rate in these animals as compared to heart rates in chloralose-urethane-anesthetized dogs (24), contributed to the negative inotropic and chronotropic responses to PGB compounds. PGB compounds increased PAP and RVP without any measurable increases in LVEDP. PGB_2-induced increases in PADP were greater than PGB_2-induced changes in PSP. These findings are consistent with the conclusion that PGB-induced increases in pulmonary pressure are mediated by pulmonary smooth muscle constriction. PGB_2-induced cutaneous vasoconstriction is not reflexly mediated due to activation of sympathetic discharge since ia administration of this prostaglandin, directly into the paw, results in vasoconstriction. Finally, PGB_2 is a more potent constrictor substance than PGB_1. This may result from a greater potency of PGB_2 or because more of this PG passes through the lungs than PGB_1.

The results of the present study leave many unanswered questions concerning the actions of PGB on the cardiovascular system. However, the cutaneous, cardiopulmonary and renal actions of these prostaglandins are now under separate and intensive investigation in this laboratory. The findings clearly demonstrate that PGB compounds are not inactive metabolites as previously considered but have activity distinct from the other prostaglan-

dins. The ability of PGB compounds to cause an increase in pulmonary pressure, and probably pulmonary vascular resistance, would not have been anticipated from the observed hypotensive effects on systemic administration. PGA compounds are utilized experimentally as antihypertensive agents (22–23), with the assumption that the observed effects in man are mediated by the PGA compounds only. Man may possess prostaglandin isomerase and convert PGA to PGB compounds. Since PGB compounds are not inactive, caution should be used, and the possible side effects of PGB compounds realized, when PGA compounds are used experimentally in man. Furthermore, until the pharmacology of the PGB compounds is elucidated and the extent of conversion of PGA to PGB (in man) is known, PGA should not be utilized in patients with pulmonary hypertension or impaired myocardial function.

Summary. The effects of intravenous PGB_1 and PGB_2 on systemic pressure, HLPP, HP PP, PAP and LVP were evaluated in intact anesthetized dogs. Both PGB_1 or PGB_2 decreased SAP, LVP and HR but did not affect either RAP or LVEDP. These PGB-induced decreases in systemic pressure probably reflected the decreased LVP as well as vasodilatation in the renal bed. Since PGB_1 and PGB_2 both increased PAP without increased LVEDP, the data suggest that these prostaglandins increased the resistance across the lungs. Furthermore, PGB_2 was a potent constrictor of the perfused canine hindpaw when administered intra-arterially into the paw or intravenously. The data are compatible with the conclusion that PGB_1 and PGB_2 possess vasodilator and vasoconstrictor activity on the canine cardiovascular system. PGB_2 is a more potent prostaglandin than PGB_1.

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