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Prostacyclin (PGI_2) Elicits Reflex Bradycardia in Dogs: Evidence for Vagal Mediation (40625)

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Prostacyclin (PGI_2), the recently discovered naturally occurring product of arachidonic acid (AA) metabolism when injected into the dog causes a reduction in both heart rate and blood pressure (1). Since other prostaglandins (PG) have been shown to stimulate cardiovascular afferent neurons in the lung and heart (2) and since reflex reductions in heart rate occur following the injection of veratrum alkaloids (3), bradykinin (4), and episodes of myocardial ischemia (5), we speculated that the bradycardia induced by PGI_2 might also be reflex in origin. The current study describes the cardiovascular effects of PGI_2 and provides evidence that the PGI_2-induced bradycardia is a reflex that originates with the stimulation of cardiopulmonary receptors and is mediated by vagal nerve fibers.

Methods. Preparation of animals. Thirty-three male mongrel dogs (17–35 kg) were anesthetized with a mixture of equal amounts of Dial-urethane (Ciba–Geigy) and Nembutal (Abbott). Either the thorax was opened in the fourth left intercostal space for the placement of electromagnetic flow probes (Carolina Medical) and pressure cannulas in open-chest dogs as previously reported (6) or catheters and a catheter-tippped flow probe were advanced into the left ventricle and aorta for the measurement of left ventricular pressure and cardiac output, and into the pulmonary artery for pressure recording and the injection of drugs in closed-chest animals. Systemic blood pressure was measured from a cannula in the brachial artery, and heart rate was calculated from the pressure pulse interval electronically (Narco). Maximum dP/dt was derived from the ventricular pressure recording and used as an indication of cardiac contractility. All data were recorded on a direct-writing oscillograph (Physiograph 6B, Narco). The animals were intubated and artificially respirated (Harvard Instruments Co.), warmed with a water-circulating heating system (Thermo-rite), and allowed at least 30 min to stabilize before injections of various agents.

Preparation of drugs. Stock solutions of PGI_2 were prepared fresh every day in 1 *M* Tris buffer (pH 9.3) at a concentration of 1 mg/ml and diluted just prior to injection in 50 m*M* Tris (pH 7.8). Arachidonic acid (Nu-chek) and PGs were prepared as sodium salts at concentrations of 1 mg/ml and diluted just prior to use in normal saline. Injections of vehicles were without effect.

Statistical analysis was performed using Student's *t* test for paired values (7).

Results. Intravenous administration of PGI_2 (1–30 μg) caused a fall in blood pressure and heart rate accompanied by a reduction in left ventricular systolic pressure, pulmonary artery pressure, and maximum dP/dt, together with an increase in cardiac output (Fig. 1). In 9 of 13 closed-chest and 15 of 20 open-chest dogs PGI_2 induced a fall in heart rate from 170 ± 5 to 151 ± 6 (mean ± SE) and 162 ± 5 to 144 ± 5 beats/min, respectively (Table I). Additionally, in open-chest dogs, injection of PGI_2 caused a 103% increase in stroke volume (10.2 to 20.7 nl) with a 9% increase in stroke work (1700 to 1950 g·cm/stroke). There was a 69% reduction in total peripheral resistance (5924 to 1875 dyne·sec/cm^5) and a 66% reduction in pulmonary vascular resistance (982 to 431 dyne·sec/cm^5). The 75% increase in cardiac output (1650 to 2890 ml/min) was achieved at a 3% reduction in cardiac work (2.75 to 2.67 kg·m/min), indicating an improved cardiac efficiency. (Above values derived from Table I.)

Increasing the dose of PGI_2 did not consistently increase the maximum fall in heart rate; however, there was a threshold dose of PGI_2 that differed from dog to dog. Also, once a response was elicited in a dog, it was reproducible throughout the experiment. In

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the dogs that did not exhibit the bradycardia to PGI_2, there was either no increase in heart rate or the increase was less than that seen to a comparable fall in blood pressure caused by nitroprusside or PGE_2. Injection of PGE_2 and PGE_1 (50 μg), both potent vasodepressors in the dog, induced as expected a reduction in blood pressure that was closely followed by a baroreceptor-mediated increase in heart rate (8). Nitroprusside (500 μg), a drug whose systemic and pulmonary vascular activity is similar to PGI_2 (9), was administered into the pulmonary artery of dogs to establish whether dilation of pulmonary blood vessels per se might be responsible for a fall in heart rate. As with PGE_2, injection of nitroprusside always resulted in a fall in left ventricular and systemic blood pressures, followed by increases in heart rate and in maximum *dP/dt*, a pattern of responses characteristic of the effects on baroreceptors of lowering blood pressure in anesthetized dogs (Fig. 2).

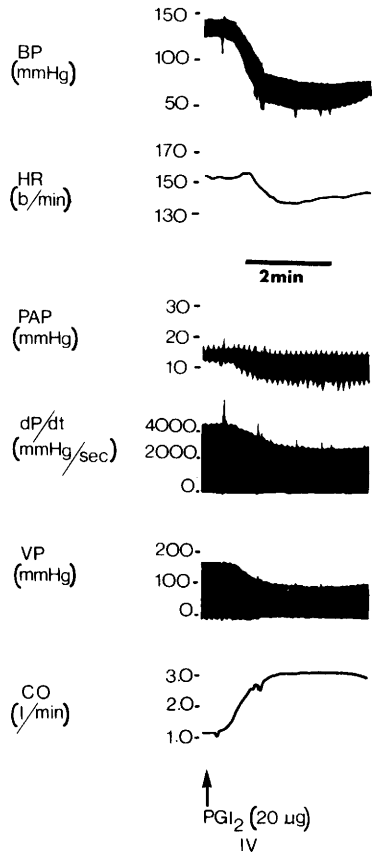

FIG. 1. The intravenous injection of PGI_2 (20 μg) into the anesthetized open-chest dog caused a fall in blood pressure (BP), heart rate (HR), pulmonary artery pressure (PAP), maximum *dP/dt*, ventricular pressure (VP), and an increase in cardiac output (CO).

Administration of PGI_2 into the pulmonary artery (Fig. 2), the brachial or femoral veins, the left circumflex coronary artery, and the left atrium or the left ventricle, all elicited bradycardia despite the acute and profound reduction in blood pressure in both open- and closed-chest anesthetized dogs. On the other hand, a baroreceptor-induced tachycardia resulted from the injection of equivalent amounts of PGI_2 into the carotid artery and the ascending or descending aorta (13 ± 3.1 beats/min and 22.6 ± 6.5 beats/min increase in the open- and closed-chest dogs, respectively) (Fig. 3) suggesting that the bradycardia is not brought about by a direct effect on peripheral baroreceptors or chemoreceptors but on an as yet undefined population of cardiopulmonary receptors. Arachidonic acid (1–5 mg), the fatty acid precursor of the 2-

TABLE I. HEMODYNAMIC CHANGES IN OPEN-CHEST DOGS INDUCED BY PGI_2[a]

	Heart rate (beats/min)	Mean arterial blood pressure (mm Hg)	Cardiac output (liters/min)	Mean pulmonary artery pressure (mm Hg)	*dP/dt* (mm Hg/sec)	Systolic ventricular pressure (mm Hg)
Control	162.3 ± 5.5 (15)	122.5 ± 5.5 (15)	1.65 ± 0.29 (13)	20.3 ± 1.6 (15)	4986 ± 330 (7)	139.0 ± 8.5 (7)
PGI_2	144.4 ± 5.3 (15)	67.9 ± 4.0 (15)	2.89 ± 0.41 (13)	15.6 ± 1.4 (15)	3686 ± 233 (7)	93.0 ± 6.9 (7)
Percentage change	−11	−45	+75	−23	−26	−33

[a] Depicted are the peak changes caused by the lowest effective dose of PGI_2 for reduction of heart rate in each dog. Values shown are mean ± SE. Number of dogs in parentheses. All changes following injection of PGI_2 are significantly different from control ($P < 0.0001$).

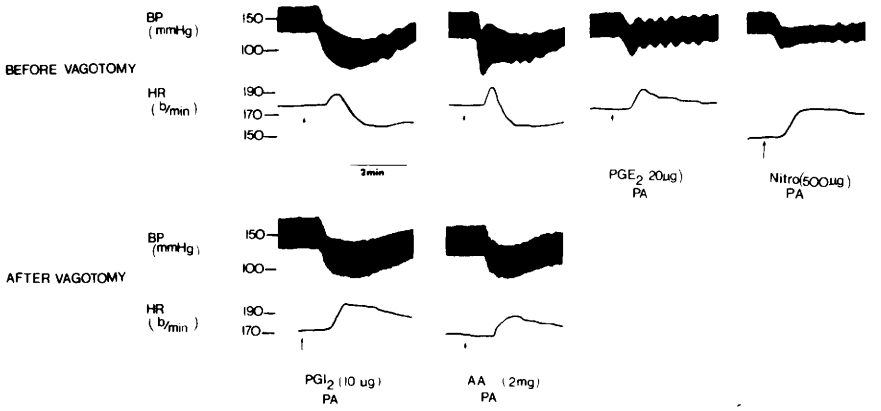

FIG. 2. Injection of PGI$_2$ or arachidonic acid (AA) into the pulmonary artery (PA) of a dog caused a fall in blood pressure concomitant with a reduction in heart rate. The transient increase in heart rate that precedes the bradycardia is only occasionally observed. PGE$_2$ and nitroprusside (Nitro) reduce pressure and increase heart rate. Vagotomy abolishes the fall in heart rate to PGI$_2$ and AA. On the other hand, vagotomy leaves the heart rate response both to PGE$_2$ and nitroprusside unchanged (not shown). The above records are from a single dog.

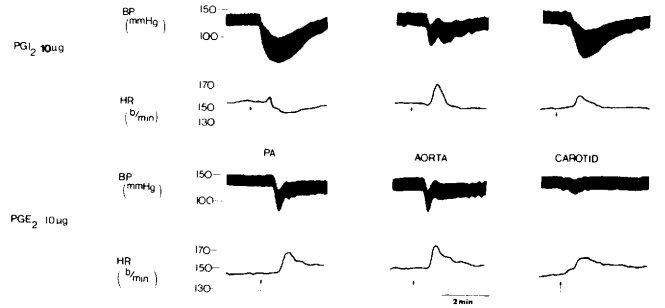

FIG. 3. Injection of PGI$_2$ into the pulmonary artery (PA) causes hypotension and bradycardia. Injections into the aorta and carotid artery result in tachycardia and a blood pressure fall which is significantly less than that seen with PA injection. Regardless of the site of the injection PGE$_2$ always induces a reduction in blood pressure that is accompanied by an increase in heart rate. The above record is from a single, closed-chest dog.

series prostaglandins, when injected into dogs not only caused a reduction in blood pressure due to the production of PGs (10) but also induced a bradycardia similar to that caused by PGI$_2$ (Fig. 2). Moreover, 6-oxo-PGF$_{1\alpha}$ (100–500 μg), the major metabolite of PGI$_2$, had no effect on blood pressure or heart rate; hence, the bradycardia is most likely due to PGI$_2$ and not to its breakdown products.

Bilateral cervical vagal section (Fig. 2) or the administration of atropine (1 mg/kg) eliminated the cardiac slowing that follows the injection of PGI$_2$ or arachidonic acid (11, 12) and allowed the typical baroreceptor-mediated increase in heart rate, that follows the lowering of blood pressure, to appear. These results confirm that the bradycardia is not due to a direct effect of PGI$_2$ on cardiac pacemaker cells but rather is reflexly mediated by vagal fibers. Moreover, vagotomy (Fig. 2) or intraaortic injection (Fig. 3) attenuated the mean blood pressure fall to prostacyclin (50.6 ± 3.8 to 37.0 ± 3.0 and to 28.6 ± 1.4 mm Hg, respectively) indicating that in addition to the direct vasodilator activity a significant portion of the vasodepressor effect of PGI$_2$ is due to a reflex reduction in peripheral resistance that is perhaps partially attributable to an inhibition of the baroreceptor-mediated increase in peripheral vascular tone.

Discussion. Prostacyclin like other vasodilator prostaglandins reduces blood pressure (13), but unlike PGE$_1$ or PGE$_2$ it also lowers significantly pulmonary artery pressure (9). These actions depend primarily on the direct

effects of PGI_2 on vascular smooth muscle (14) but also, as our experiments suggest, on a reflex reduction of peripheral resistance. This sudden decrease in afterload leads to falls in ventricular systolic pressure and cardiac contractility (max dP/dt), and also to an increase in venous return. Thus, in spite of a reduction in heart rate, cardiac output, due to an enlarged stroke volume, increases significantly.

Nitroprusside is a clinically useful agent, since it decreases pressure in both the pulmonary and systemic circulations and consequently affects the pressure–volume interrelationship of the ventricles by reducing afterload (15). Prostacyclin has vasodepressor activity similar to nitroprusside (9) thus decreasing cardiac work; additionally, since PGI_2 reduces heart rate, it may further lower myocardial O_2 consumption.

The cardiovascular profile of PGI_2, especially the effects on blood pressure and heart rate, is similar to that of veratrine as initially reported by von Bezold and Hirt (16) and later confirmed by Jarisch and Richter (17). The receptors responsible for the "Bezold–Jarisch" effect have been localized to the left ventricle (18) and the coronary circulation particularly the area supplied by the left circumflex coronary artery (3, 5). Stimulation of these receptors leads to an increase in the firing of vagal c-fibers (19) and a reduction in heart rate which is abolished by vagotomy (20). The physiologic function of these receptors may be to prevent ventricular overload (20) and, by reducing both afterload and heart rate, to decrease cardiac work during myocardial ischemia (21).

It has recently been established that PGI_2, produced by vascular endothelial cells, is a potent antiplatelet aggregatory substance (22). In addition to its dilator effect in the coronary vascular bed (23), infusion of PGI_2 into the cat following coronary ligation has been shown to stabilize lysosomes and aid in the opening of collaterals and thus protect against myocardial ischemic injury (24). Finally, since prostaglandin production under normal physiologic conditions is low, the reflex reduction of heart rate we observed may have only limited import; however, since PGI_2 is probably a circulating hormone (25) and since during injury due to ischemia, trauma, or other types of tissue injury, prostaglandin production is enhanced (26), this reflex may be of primary pathophysiologic importance. Additionally, it may serve to explain the bradycardia observed during cardiogenic shock (27), coronary arteriography (28), administration of acetylstrophanthidin (29), posterior infarction (30), and myocardial ischemia (31).

Summary. Administration of the vasodepressor prostaglandins, PGE_1 and PGE_2, and of nitroprusside, an agent whose direct vascular activity is similar to prostaglandins, resulted in a reduction in systemic arterial blood pressure accompanied by the expected reflex increase in heart rate. Injection of prostacyclin (PGI_2) and the prostaglandin precursor, arachidonic acid, into the femoral vein, pulmonary artery, left atrium, and left ventricle of the dog elicited a fall in blood pressure and a concomitant reduction in heart rate in both open- and closed-chest anesthetized dogs. Bilateral vagal section eliminated the bradycardia thus establishing that the PGI_2-induced change in heart rate is reflex in origin.

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