Metabolism of Prostaglandins A_1 and E_1 in Man

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ABSTRACT To investigate the in vivo whole blood metabolic clearance rates and sites of metabolism of prostaglandins A_1 and E_1 in man, constant infusions of the tritiated compounds were administered to normal subjects and to patients undergoing cardiac catheterization. The whole blood metabolic clearance rate of [^{3}H]prostaglandin A_1 in eight men was 5,003±864 liters/day (SD) or 2,546±513 liters/day per m^2 (SD). Nonradioactive prostaglandin A_1 was similarly infused in two subjects, and the metabolic clearance rates were determined, utilizing a specific radioimmunoassay. The clearance rates with this method correlated closely with those determined by the isotope infusions. Extraction studies of prostaglandin A_1 showed that pulmonary, splanchnic, renal, and extremity perfusions resulted in 8.1±4.1, 56.1±10.1, 50.3±3.4, and 34.4±5.9% (SEM) removal, respectively. With [^{3}H]prostaglandin E_1, the whole blood metabolic clearance rate was determined from the pulmonary artery concentration in three patients and averaged 4,832±1,518 liters/day (SD) or 2,686±654 liters/day per m^2 (SD). Pulmonary extraction was 67.8±6.8% (SEM) and extremity removal averaged 6.6±4.9% (SEM).

These results indicate that A prostaglandins are metabolized by several organs, such as the liver and kidney, and possibly by intravascular pathways as well. In man, the E prostaglandins are primarily metabolized by the lung, but extraction is not complete and approximately one-third may escape lung metabolism. Thus, these findings suggest that both E and A prostaglandins in the venous circulation may reach the systemic circulation in man.

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INTRODUCTION

The hypothesis that renal prostaglandins reach the arterial circulation could have important physiologic consequences. The E and A prostaglandins, when infused intravenously at some doses, have natriuretic and vasodepressor actions (2). However, at certain infusion rates, prostaglandin A_1 (PGA_1)[1] appears to selectively stimulate aldosterone secretion (3, 4). This suggests the possibility that A or E prostaglandins and angiotensin II could act in concert to regulate mineralocorticoid production while antagonizing each others effect on blood pressure (5). The presence of circulating prostaglandins could therefore have important effects upon both blood pressure and fluid volume control.

In the cat and dog, it has been demonstrated that E prostaglandins are rapidly metabolized by the lung, whereas A prostaglandins appear to escape this degradation (6, 7). This difference in metabolsim has led to the speculation that A prostaglandins may function as circulating hormones. In man, Hamberg and Samuelsson have shown that tritiated prostaglandin E_2 (PGE_2), injected as a bolus, is rapidly cleared from the circulation with the formation of the less polar metabolite, 13, 14-dihydro-15-keto PGE_2, in blood (8). As pulmonary tissue contains the enzymes necessary for this conversion (9), it has been presumed that the lung is the first organ of metabolism of E prostaglandins, and this has recently been confirmed in vivo in the dog (10). Studies of the clearance of A prostaglandins from the human circulation or the sites of this removal have not been available.

[1] *Abbreviations and trivial names used in this paper:* MCR, metabolic clearance rate: PG, prostaglandin; PGA_1, prostaglandin A_1 (15-hydroxy-9-ketoprosta-10,13-dienoic acid); PGA_2, prostaglandin A_2 (15-hydroxy-9-ketoprosta-5,10,13-trienoic acid); PGE_1, prostaglandin E_1, (11α,15-dihydroxy-9-ketoprost-13-enoic acid); PGE_2, prostaglandin E_2 (11α,15-dihydroxy-9-ketoprosta-5,13-dienoic acid); 13, 14-dihydro-15-keto PGE_2, 11α-hydroxy-9,15-diketoprost-5-enoic acid.

This study was designed to determine the metabolic clearance rate in blood and the major in vivo sites of metabolism of PGA_1 and PGE_1 in man.

METHODS

Materials. Spectrograde methanol and dichloromethane were purchased from Matheson Coleman & Bell (East Rutherford, N. J.).

[^{3}H]PGA_1 (sp act 384.6 μCi/μg), [^{3}H]PGE_1 (sp act 312.5 μCi/μg), and [^{14}C]PGE_1 (sp act 1.41 μCi/μg) were purchased from New England Nuclear (Boston, Mass.). [^{14}C]PGA_1 was chemically converted from [^{14}C]PGE_1 by acidification according to the method of Andersen (11) and then purified by an LH-20 Sephadex chromatography system as previously described (12).

Radiochemical purity. The radioactive prostaglandins were periodically checked for purity by the demonstration of a single elution peak from an 80 × 1-cm LH-20 Sephadex column using the system methylene chloride, methanol (95:5). In addition, the [^{3}H]PGA_1 was checked against [^{14}C]PGA_1 by mixing quantities of them together. An aliquot of the mixture was counted and the remainder was chromatographed. The "A fraction" (from 65 to 85 ml) was collected and counted. (Original ^{3}H/^{14}C ratio: 4.10; chromatographed ratio: 4.08.) Similarly, [^{3}H]PGE_1 and [^{14}C]PGE_1 were mixed, and an aliquot was chromatographed with collection and counting of the "E fraction" (105–135 ml). (Original ^{3}H/^{14}C ratio: 3.84; chromatographed ratio: 3.75.)

Subjects. The metabolic clearance rate (MCR) of PGA_1 was determined in five healthy men who gave informed consent.

Studies of the sites of metabolism of both PGA_1 and PGE_1 were performed on 10 patients (6 men and 4 women) who were scheduled for elective cardiac catheterization. All the patients were given a full explanation of the study, and all volunteered to participate. At the time of the study, the patients were clinically stable with no evidence of congestive heart failure, hypertension, or significant regurgitant valvular lesions. Serum creatinine and liver function tests were normal. The cardiac index of these patients was only slightly reduced, averaging 2.9 liters/min per m^2. The cardiologic diagnoses are presented in Table III.

Constant infusion method. Constant rate infusions of [^{3}H]PGA_1 and [^{3}H]PGE_1 were performed in a manner similar to that employed for the determination of the metabolic clearance rates of various steroids (13). All infusions were administered to the subjects in the morning, after an overnight fast. The patients maintained the supine position throughout the infusion period. Infusion solutions were prepared by dissolving 20 μCi of [^{3}H]PGA_1 or 80 μCi of [^{3}H]PGE_1 in 4 ml of absolute ethyl alcohol and then diluting this in 50 ml of normal saline. The infusions were begun in an antecubital vein with a 10% priming dose of this solution and they were continued at a rate of 0.382 ml/min (infusion pump, Harvard Apparatus Co., Inc., Millis, Mass.). The calibration of the pump was monitored and found to be accurate. During the infusions, 5 ml of heparinized whole blood was collected on ice from the opposite arm at 90, 105, and 120 min. At the conclusion of each study, infusion fluid was collected from the patient's intravenous tubing. As the concentration of tritiated prostaglandin in this fluid was nearly identical to that calculated from the amount of counts and diluent added, it did not appear that there was appreciable adsorption of the labeled prostaglandins onto the surfaces of the infusion system. Samples of the infusion solution were rechromatographed and retained their characteristic elution pattern.

In two subjects, the MCR was also calculated by infusions of nonradioactive PGA_1. The first study was performed by the infusion of four different doses for 1-h periods. At the end of each period, blood was obtained for the measurement of PGA_1 concentration with a specific radioimmunoassay (14). The infusion fluid was appropriately diluted and measured in the same radioimmunoassay. The second subject's MCR was calculated from a 1-h infusion of a single dose of nonradioactive PGA_1.

In the 10 catheterization studies, the constant infusions were begun in the antecubital vein as soon as the patient was positioned on the radiography table. The cardiology staff then proceeded with indicated studies with catheter positioning performed by the percutaneous technique. In all the studies, catheters were placed in the pulmonary artery and the left ventricle or ascending aorta. In four studies, a catheter was placed in the hepatic vein and in three studies in a renal vein. Blood was drawn from these catheters and a peripheral vein at 90, 105, and 120 min, when possible.

Sample handling. Whole blood was utilized because of the possibility that infused PGA_1 may diffuse into the cellular elements of blood (14). Additionally, we have reported evidence for metabolism of A prostaglandins by whole blood in vitro (15). The use of whole blood allowed the immediate introduction of the second isotope to correct for this potential in vitro source of error.

The 5-ml blood samples were collected in iced heparinized syringes and immediately lysed by addition to a 100-ml conical centrifuge tube containing 5 ml of deionized water and ^{14}C-labeled indicator (approximately 500 cpm). This mixture was acidified with the addition of 1 ml of 0.5 M phosphate buffer, pH 4.5. Extraction was quickly performed by adding 80 ml of 5% methanol in dichloromethane and shaking vigorously. After centrifugation at 2,000 rpm for 10 min, the aqueous layer was decanted, and the organic solvent was separated from the overlying precipitate by filtration through glass wool and anhydrous sodium sulfate. After the organic solvent was evaporated in a vacuum apparatus (Rinco Instruments Co., Inc., Greenville, Ill.), the samples were chromatographed on a Sephadex LH-20 system (12). The A fraction (from 65 to 85 ml) or E fraction (105–135 ml) was collected, dried under nitrogen, and counted in 10 ml of 2,5-diphenyloxazole-1,4-bis[2-(5-phenyloxazolyl)]benzene (Spectrafluor, Amersham/Searle Corp., Arlington Heights, Ill.) in toluene with a Mark I dual channel scintillation counter (Nuclear-Chicago Corp., Des Plaines, Ill.) (^{3}H efficiency, 35%. ^{14}C efficiency 68%; ^{14}C to ^{3}H feedthrough, 15%). Samples were counted for a period long enough to reduce the error of counting to less than 2% (40 min, three times) (16). The recoveries for PGA_1 and PGE_1 averaged 44.9% (38.3–55.3) and 34.2% (30.5–41.4), respectively.

The purity of the chromatographic peaks was demonstrated on several studies by fractionation of the collection of the peaks and showing uniformity of the ^{3}H/^{14}C ratio.

When plasma measurements were made, iced heparinized blood was immediately centrifuged at 0°C for 10 min at 2,000 rpm. Rapid preparation of the plasma was felt to be critical in minimizing in vitro metabolism. The extraction procedure for plasma was identical to that of whole blood.

Calculations. Whole blood MCRs were determined by the formula MCR (liters/day) = infusion rate (counts/day)/whole blood concentration (counts/liter). The infusion rate was calculated by counting several 0.1-ml dried samples of infusion fluid and multiplying by the infusion

rate of the pump. The whole blood concentration of tritiated prostaglandin was determined from the counts of the appropriate chromatographic fraction by subtracting the counts due to background and ^{14}C–^{3}H feedthrough and correcting for losses as calculated from the ^{14}C counts.

The concentration of prostaglandin counts at various points in the circulation was used to calculate the extraction accomplished by the circulation through several organs. Thus, the percent extracted by the lung was equal to: (pulmonary artery concn.)-(left ventricle concn.)/(pulmonary artery concn.) × 100. The percent extracted by a peripheral organ was equal to: (left ventricle concn.)-(venous drainage of organ concn.)/(left ventricle concn.) × 100.

The clearance rate of an organ was calculated as the product of the extraction fraction and the estimated blood flow through the organ in the basal state.

RESULTS

MCRs. The whole blood MCR of PGA_1 in five normal men was 5,052±914 liters/day (SD). When expressed in terms of body surface area, the value was 2,600±482 liters/day per m^2 (SD). In three men undergoing catheterization for cardiac diagnosis, the same calculations could be performed, and no significant difference in the data was noted. The overall MCR in the eight men was 5,003±864 liters/day (SD) or 2,546±513 liters/day per m^2 (SD) (Table I). The MCR of PGA_1 was calculated in only one woman (M. F.), a cardiac patient with a slightly decreased cardiac index. Her MCR of 2,469 liters/day or 1,543 liters/day per m^2 was the lowest individual value measured, although it was within 2 SDs of the mean of the male clearances when corrected for body surface area.

There was a trend in the data with an average difference of 15.8±11.2% (SD) between the 90- and 120-min samples. As a priming dose was used, failure to reach equilibrium should be reflected by falling concentrations. The actual trend was in the opposite direction and may reflect a recirculation effect or a changing cardiac output. The latter was felt to be the major factor in the greater variability seen in those patients undergoing cardiac catheterization. In one subject (D. R.), the infusion was extended to a total of 4 h and additional samples were drawn at 210 and 240 min. The MCR calculated at 90 min differed only by 5.9% from that determined at 240 min. The maximum variation from the mean of all five samples was 6.1%. This indicates that equilibrium most probably had been reached by 90 min, as would be expected of a compound with a high MCR, and that the method was reproducible with the subject in a basal state.

Aside from the PGA_1 region, no significant tritium was eluted from the chromatography columns in these studies except for a minor (< 5%), less polar peak.

In a healthy man (G. B.), 1-h infusions of four different doses of nonradioactive PGA_1 were used to calculate the MCR. The MCR results (Table II) were consistent at all four doses, with a maximum variation of 7.5% from the mean. The average MCR of the four infusion rates was 5,784±363 liters/day (SD) or 3,324±

TABLE I

MCR of [^{3}H]PGA_1

Subject	Sex	Age	Infusion rate	Blood counts/liter × 10^{-3}				MCR	MCR
				90 min	105 min	120 min	Mean		
		yr	*counts/day* ×10^{-8}					*liter/day*	*liters/day per* m^2
Normal subjects									
G. L.	M	26	1.39		28.4	32.7	30.6	4,562	2,258
M. T.	M	26	1.47	37.9		37.7	37.8	3,889	2,102
N. R.	M	30	1.04	15.2	17.9	18.7	17.3	6,099	3,227
R. H.	M	41	1.12	22.1		23.7	22.9	4,870	2,435
D. R.	M	36	2.01	33.8	36.6	36.5	35.5*	5,841	2,980
							Mean (±SD)	5,052±914	2,600±482
Catheterized patients									
R. B.	M	45	1.75	28.7	32.0	37.8	32.8	5,411	2,552
V. G.	M	26	1.75	40.5	49.2	49.1	46.3	3,813	1,749
V. R.	M	41	1.79		32.3	32.3	32.3	5,540	3,061
							Overall mean (±SD)	5,003±864	2,546±513
Female patient									
M. F.	F	56	1.62	58.6	69.1	70.4	66.0	2,469	1,543

* Includes values from 210 and 240 min.

TABLE II

MCR of Nonradioactive PGA_1

Subject	Infusion rate	PGA_1 concentration by radioimmunoassay*	MCR
	μg/day	*μg/liter*	*liters/day*
G. B.	7,020	1.19	5,899
	14,040	2.59	5,421
	28,080	4.50	6,240
	56,160	10.07	5,577
		Mean (±SD)	5,784±363
D. R.	7,401	1.21	6,117

* Endogenous concentration of 0.028 μg/liter (G. B.) and 0.025 μg/liter (D. R.) subtracted.

209 liters/day per m^2 (SD). Simultaneous plasma concentrations were measured at the completion of two of the infusions, and the values were very similar to the whole blood concentrations (1.23 vs. 1.19 μg/liter and 5.01 vs. 4.50 μg/liter), suggesting that PGA_1 distributes equally throughout blood. In a second subject (D. R.), the MCR via the nonradioactive technique was 6,117 liters/day compared to 5,841 determined previously by the isotopic method; a difference of only 5%.

The whole blood MCR of PGE_1 could not be determined from peripheral blood concentrations as this site is distal to a major organ of metabolism (the lung). When the pulmonary artery concentration was used to calculate the MCR, the average in three cardiac patients was 4,832±1,518 liters/day (SD) or 2,686±654 liters/day per m^2 (SD).

Organ extraction and clearance of PGA_1 and PGE_1. In seven studies, extraction of PGA_1 by the lung averaged 8.1±4.1% (SEM), which was not statistically different from 0, ($P > 0.05$). In contrast, sampling from the venous drainage of the liver, kidney, and extremities showed significant extraction by these organs. The extraction by the splanchnic circulation averaged 56.1±10.1% (SEM) in four patients ($P < 0.05$), the renal extraction was 50.3±3.4% (SEM) in three patients ($P < 0.01$), and the extremity extraction was 34.4±5.9% (SEM) in six patients ($P < 0.01$). (Fig. 1 and Table III).

Organ clearance of PGA_1 was calculated as the product of extraction and blood flow through each organ, assuming a basal cardiac output of 3.3 liters/min per m^2 (4,752 liters/day per m^2) (17) and that the perfusion of the pulmonary, splanchnic and renal circulations represented 100, 38, and 20%, respectively, of the cardiac output (18, 19). The averages were: pulmonary clearance 270 liters/day per m^2; splanchnic clearance, 700 liters/day per m^2; and renal clearance, 330 liters/day per m^2. Thus, the total clearance attributable to the pulmonary, splanchnic, and renal circulations totaled 1,300 liters/day per m^2, only slightly more than half of the total clearance.

In three patients, the pulmonary extraction of infused tritiated PGE_1 averaged 67.8±6.8% (SEM) ($P < 0.01$). The extraction of the upper extremity averaged 6.6±4.9% (SEM) ($P > 0.05$) (Fig. 1 and Table III).

DISCUSSION

In several species, the biologic potencies of E prostaglandins have been found to be much greater via intra-aortic injection than by the intravenous route (20, 21). Thus, it became clear that the lung probably played a major role in degrading these compounds. The blood-bathed organ perfusion technique subsequently confirmed the capacity of the lung to metabolize E and F prostaglandins (22). However, the A prostaglandins have nearly equal effects when injected intra-arterially or intravenously (6, 7). The action of the enzyme 15-hydroxyprostaglandin dehydrogenase appears to be the first step in the degradation of E and F prostaglandins. This enzyme, which metabolizes A prostaglandins at a somewhat slower rate (23), has been found in high concentrations in the lung, spleen and kidney cortex of the pig (24). The 15-keto derivatives of E and F prostaglandins may be further modified by reduction at the 13, 14-double bond by a reductase enzyme present in several tissues of the swine (9). The 13,14-dihydro-15-keto derivative of PGE_2 was found to accumulate rapidly in the blood of man after an intravenous injection of the tritiated prostaglandin (8). Further metabolism of the E and F prostaglandins appears to be oxidative

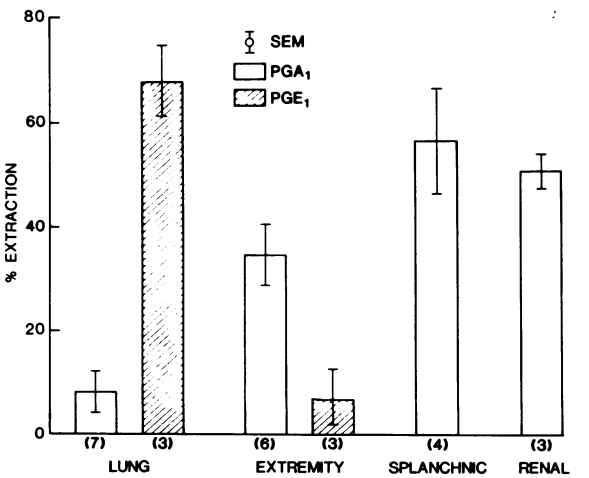

FIGURE 1 Percent extraction of PGA_1 and PGE_1 by perfusion of the lung, extremity, splanchnic region, and kidney. Numbers in parentheses indicate number of studies performed.

TABLE III

Extraction Studies of [^3H]PGA_1 and [^3H]PGE_1

Subject	Sex	Age	Diagnosis	Sites counts/liters × 10^{-3}*					Extraction, %			
				Pulmonary artery	Left ventricle	Peripheral vein	Hepatic vein	Renal vein	Pulmonary	Extremity	Splanchnic	Renal
[^3H]PGA_1												
M. F.	F	56	Mitral stenosis Atrial fibrillation	121.4	93.5	66.0	53.4		23.0	29.3	42.3	
R. B.	M	45	Angina	50.8	45.3	32.8	13.8		10.8	27.5	69.5	
F. W.	M	37	Ventricular aneurysm	41.9	43.3	19.5‡	10.1		0	55.0‡	76.7	
V. G.	M	26	Ventricular aneurysm	52.8	56.8	46.3	36.5		0	13.6	35.7	
M. P.	F	29	Prosthetic mitral valve Atrial fibrillation	123.8	95.2			48.5	23.1			49.1
K. H.	M	43	Angina	47.7	48.5	26.5‡		21.0	0	45.4‡		56.7
V. R.	M	41	Mitral stenosis	49.8	50.1	32.3		27.5	0	35.5		45.1
							Mean (±SEM)		8.1±4.1	34.4±5.9	56.1±10.1	50.3±3.4
							P§		>0.05	<0.01	<0.05	<0.01
[^3H]PGE_1												
C. B.	F	71	Mitral stenosis	136.2	62.1	52.1			54.4	16.1		
W. R.	M	62	Angina	82.4	19.5	18.8			76.3	3.6		
L. F.	F	51	Angina	138.3	37.7	38.1			72.7	0		
							Mean (±SEM)		67.8±6.8	6.6±4.9		
							P§		<0.01	>0.05		

* Mean value of determinations at 90, 105, and 120 min.
‡ Peripheral blood obtained from the femoral vein.
§ Values compared to 0.

with the formation of polar metabolites which are cleared into the urine. The liver, a source of oxidative enzymes, is also capable of inactivating a large fraction of E and A prostaglandins in single passage perfusion studies in the cat (6).

Little is known of the metabolic pathway for PGA degradation, but the kidney is a potential organ of metabolism. In the rabbit, injection of PGA_2 into the renal artery has resulted in quantitative conversion to less polar metabolites in the renal venous blood (25).

Enzymes in the blood may also play a role in prostaglandin interconversions and degradation. Jones and Cammock have demonstrated that the plasma of several species is capable of converting A to B prostaglandins, probably with C prostaglandins as an intermediary product (26). However, in recent studies it has been shown that the reaction rates of A to C isomerization and E to A conversion are quite slow in human serum (27). In vitro studies with whole blood in our laboratory indicate that the cellular elements of the blood may be capable of metabolizing A prostaglandins (15).

The existence of A prostaglandins in vivo remains an open question (28, 29). Although several radioimmunoassays measure A prostaglandins, a recent study with gas chromatography-mass spectrometry was unable to detect PGA_2 in human plasma (sensitivity of 200 pg/ml) (30). If they are present, A prostaglandins may result from the enzymatic conversion of E prostaglandins. Robertson has reported that the infusion of PGE_2 in man elevates plasma radioimmunoassayable prostaglandin A concentrations (31). In the present study, chromatography of the blood extracts from the [^{3}H]-PGE_1 infusions demonstrated the presence of three peaks, one with the mobility of [^{3}H]PGE_1 and two that were less polar. The larger and more polar of these two other peaks had a mobility similar to that of an A prostaglandin. An antibody quite specific for PGA_1 (14) was added in high concentration to the counts of this peak, and the bound fraction was precipitated with ammonium sulfate. Compared to [^{3}H]PGA_1, the counts of this peak were only partially precipitated with the antibody.

Two methods were used to measure the clearance rate of PGA_1 in this study. The infused dosage (0.125-1.0 μg/kg per min) of nonradioactive PGA_1 has been shown to increase renal blood flow (2) and was observed to increase the pulse without changing the blood pressure in our subjects. Although the clearance rate was similar for four different infusion rates, the biological activity of this material could have influenced the clearance rate. However, this method verified the results obtained with the radioactive method in which tracer quan-

tities were infused (less than 25 ng/h of PGA_1 and less than 125 ng/h of PGE_1). No changes in pulse or blood pressure were observed with these infusions.

The results of the present study indicate that the clearance rates of PGA_1 and PGE_1 are quite high, in excess of the blood flow to any organ except the heart and lung. The identification of the extracted isotopes was made chromatographically. Thus, if there were conversion to a metabolite with nearly identical chromatographic properties (i.e. A to B isomerization), this technique would not recognize this metabolism. In this sense, the calculated MCR represents a minimal value.

In this context, the high clearances of PGA_1 and PGE_1 would lead us to predict that these compounds are cleared either by pulmonary metabolism or by metabolism in multiple organs. A third possibility could be intravascular metabolism. In addition, the high clearances would be compatible with the previously demonstrated low affinity albumin binding of these substances (*32*).

The extraction studies have demonstrated that man metabolizes E and A prostaglandins in different ways. With PGA_1, there was minimal evidence of pulmonary clearance, but perfusion of the splanchnic and renal circulations resulted in significant extraction. As these extractions can explain only a portion of PGA_1 clearance, these findings can be interpreted to indicate that multiple peripheral organs are involved in the metabolism of PGA_1. However, the extraction in the extremities and the demonstrated capacity of the blood to metabolize A prostaglandins in vitro suggests that intravascular metabolism may also play a role.

In contrast, the studies with PGE_1 showed that the lung was a major organ of metabolism and that there was little or no extraction by the extremities. PGE_1 in the arterial circulation presumably could be metabolized by the liver or other organs as well.

Perhaps the most significant findings of these studies was the demonstration that constant intravenous infusion of both substances resulted in the recovery of appreciable counts of the infused material in the peripheral circulation. Although the extraction of PGE_1 by the lung was considerable, it was not complete. This may be important in view of the findings that various stimuli are capable of releasing E prostaglandins into the renal vein (*29*). Thus, prostaglandins of either the A or E series, if released into the venous circulation, have the potential to reach and affect the systemic vasculature and distant organs.

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