The Prolonged Pressor Response to Renin in the Nephrectomized Rat

GRAHAM W. BOYD

SUMMARY Angiotensin I dose-response curves and renin clearances were studied in nephrectomized and paired sham-nephrectomized control rats under pentobarbital anesthesia. Both threshold and slope of the angiotensin dose-response curves were decreased 22 hours after nephrectomy. In addition, the ratio of renin clearance (determined during renin infusions) in the 22-hour-nephrectomized rat to that in paired 22-hour sham-nephrectomized controls was 0.50 ± 0.03 (mean ± SEM, P < 0.001, n = 12 pairs). The finding of reduced renin clearance was confirmed by an indirect assessment of "effective renin clearance" based on a comparison of the blood pressure decline after renin injections with angiotensin I dose-response curves in the same rat. Overall, approximately half of the 50% fall in renin clearance could be accounted for by an immediate effect of removal of the kidney on renin clearance. This role of the kidney in renin clearance was confirmed by the finding of a renal venous-arterial renin ratio of 0.9 ± 0.03 (P < 0.005) during renin infusion in normal rats. It is concluded that both changes in the angiotensin I dose-response curve and decrease in plasma renin clearance contribute to the postnephrectomy prolongation of the renin pressor response in the rat. Circ Res 45: 396-404, 1979

THE well-recognized prolongation of the pressor response to intravenously administered renin, which develops in the rat over the 24-hour period following nephrectomy, has never been explained satisfactorily. Studies on renin clearance are conflicting (Schaechtelin et al., 1964; Peters-Haefeli, 1971), and even when a decreased clearance has been found after nephrectomy (Bing and Nielsen, 1973), the magnitude of change seems insufficient
to account for the entire pressor response. Therefore, I reinvestigated this phenomenon, particularly in light of the recent observation that protein binding of renin may greatly prolong its action on blood pressure in vivo (Boyd, 1974). A report of the preliminary findings of this study has been published previously (Boyd, 1976).

Methods

White male Wistar rats, weighing 300-580 g, were anesthetized with sodium pentobarbital (Nembutal), 6 mg/100 g, ip. A neck incision was made and the trachea cannulated for administration of oxygen (approximately 0.3 ml/sec by an open circuit method). Both external jugular veins and the right common carotid artery were cannulated with polyethylene PE 60 cannulas (Clay-Adams). All rats were given 100-150 U of heparin intravenously just prior to the arterial cannulation. Temperatures were monitored with a rectal thermometer and kept between 37°C and 38.5°C throughout all experiments with an adjustable overhead 60-watt lamp. Mean arterial pressure was measured with Statham P23Db strain gauge, coupled to a Beckman dynograph recorder (type RP). In preliminary experiments, the relatively large blood pressure elevation associated with renin infusions caused a moderate degree of blood loss, particularly in nephrectomized rats. Because of this, and because such elevation of blood pressure might itself influence renin clearance, all subsequent studies of the effect of nephrectomy on renin clearance were carried out after the administration subcutaneously, of 1 mg of pentolinium tetrurate (Ansolysen), immediately before the control period. This reduced mean arterial pressure to approximately 50 mm Hg but allowed relatively normal levels of mean arterial pressure (90-130 mm Hg) during renin infusions. Surgical blood loss was now kept to a minimum. In recognition of the possibility that ganglionic blockade of this nature itself might influence the result, all experiments were paired with sham-nephrectomized controls, which also were given this drug. Basal mean arterial pressures (40-65 mm Hg) after pentolinium were similar in both groups. In addition, half of the studies on the arteriovenous difference of renin across the kidney during renin infusions were carried out in the absence of pentolinium, with no effect on the result (see below). Except where otherwise stated, all blood samples for plasma renin measurement were taken directly from the carotid artery cannula.

Bilateral nephrectomy (or sham nephrectomy) was carried out retroperitoneally through loin incisions under ether anesthesia, 15-27 hours before the experiment. Water and food were withheld overnight but offered to sham-nephrectomized rats on the morning of the experiment for 1-2 hours. Under these conditions, the weight of both sham-nephrectomized and nephrectomized rats changed very little during the 24-hour postoperative period.

Rat renin was prepared either by the method of Peart et al. (1966) up to and including the DEAE-cellulose step, or by 10% trichloroacetic acid precipitation of rat kidney homogenates at pH 2.9 (room temperature). The final solution for infusion was made up in Tris buffer, 0.02 mol/liter; NaCl, 0.13 mol/liter; neomycin sulphate, 0.3 mmol/liter, or 0.02%; and human serum albumin, 0.05 mol/liter, pH 7.5. Renin was infused intravenously via a Braun Perfusor (model 871-104) at a rate of 0.05 ml/min and in amounts sufficient to raise mean arterial pressure in sham-nephrectomized rats by 40-90 mm Hg.

Angiotensin I dose-response curves were carried out in nephrectomized and sham-nephrectomized rats using 10-minute infusions at each of five different dose levels over the range 2.5-50 pmol/min. Curves relating log dose of angiotensin infusion to the increment in blood pressure at each level then were constructed so as to compare the threshold and slope of the response in the nephrectomized rat with that in sham-nephrectomized controls. In addition, these curves were used to calculate "effective renin clearance" from the circulation by relating them to the rate of blood pressure decay following the peak response to renin injections. This allowed each point on the blood pressure decay curve, after renin injection, to be assigned a value of angiotensin I production rate in vivo, a parameter indirectly related to plasma renin concentration.

Renal Arteriovenous Renin Differences

Cannulation of the left renal vein was achieved indirectly via the left femoral vein, exposed by a left groin incision. A PE60 cannula was used and initially was positioned with the aid of radiological contrast material (Hypaque 30, 0.5 ml). Subsequently, however, with experience and with the correct curve on the cannula tip (approximately 90°), the left renal vein could be cannulated successfully without fluoroscopic control in over 80% of experiments. The cannula was always passed well out toward the renal hilum, well beyond the entrance of the left adrenal and spermatic veins. Its position was checked routinely at the end of each experiment.

Plasma Renin Concentration Assay

Rat renin substrate was prepared by dialysis of 24-40 48-hour nephrectomized rat plasma against sodium phosphate buffer, 0.025 mol/liter, pH 7.5 (containing neomycin, 0.3 mmol/liter); application to a 2 × 40-cm DEAE-cellulose column, equilibrated in the same buffer; and elution with buffer containing sodium phosphate (0.025 mol/liter) sodium chloride (0.05 mol/liter), and neomycin (0.3 mmol/liter, pH 7.5). After concentration by pressure ultrafiltration (Amicon PM10 membranes), the substrate was dialyzed against sodium phosphate buffer, 0.1 mol/liter, containing sodium chloride,
0.05 mol/liter and neomycin, 0.3 mmol/liter, pH 7.5. If assay at this stage showed appreciable "angiotensinase" activity (i.e., >20% loss of 50 ng/ml added angiotensin I over 4 hours at 37°C), the substrate was acidified to pH 4.5 with 1 mol/liter HCl for 30 minutes at 32°C and then neutralized to pH 7.5 with 1 mol/liter NaOH. The final substrate preparation contained between 20 and 30 mg/ml protein and generated between 3.0 and 6.6 ng of angiotensin I per ml with excess rat renin. Even at this relatively high substrate concentration, the amount of angiotensin I, generated per unit time with constant small amounts of added rat renin, varied (linearly) with the substrate concentration, so that for calculation of renin clearances, the standard rat renin infused was calibrated separately with each substrate preparation.

For renin concentration assay, 0.025 ml rat plasma was incubated with 0.15 ml rat renin substrate; dimercaptopropranol (BAL), 0.01 mol/liter; ethylenediaminetetraacetic acid (EDTA), 0.015 mol/liter; and phenyl-methyl-sulphonyl-fluoride (PMSF), 0.01 mol/liter in a final volume of 0.2 ml. After incubation for 4 hours at 37°C, renin was determined directly on unextracted plasma by immunoassay of angiotensin I generated (Boyd et al., 1969).

In investigating the possible existence of acid-activatable forms of inactive renin (Boyd, 1974), plasma (1 ml) taken at the end of a 45-minute renin infusion was dialyzed against Skinner A buffer at pH 3.3, 4°C overnight, neutralized [Skinner (1967) buffer C, pH 7.5, dialysis], and its renin concentration compared with that in a duplicate 1-ml sample dialyzed to pH 7.5 only [Skinner (1967) buffer C]. 

131I-Iodohippurate for measurement of renal plasma flow was obtained from the Australian Radiation Laboratories. It contained less than 0.5% free iodine and had a specific activity of 5 μCi/mg. For infusion, it was diluted in the renin solution and infused at the rate of 2.5 μCi/min. Renal plasma flow was estimated from the rate of infusion and the equilibrium (45 minutes) renal venous and arterial plasma 131I counts by the Fick formula.

Materials

Angiotensin I standard was the isoleucine5 form (Schwarz/Mann). 1125-I-ileu4-angiotensin I was obtained from the New England Nuclear Corporation. BAL, EDTA, and PMSF were Sigma products, and human serum albumin was supplied by the Commonwealth Serum Laboratories. Angiotensin II antibody was raised as described previously (Boyd and Peart, 1968) and was shown to be capable of neutralizing 1–2 μg of angiotensin II per ml on bioassay after incubation with an angiotensin II standard for 1 minute at 4°C.

Results

First, the slow development of a prolonged pressor response to intravenous injections of renin over the 24-hour period following nephrectomy was confirmed (Fig. 1). This effect was not evident during the 1st hour but appeared to develop to its maximum some 15–25 hours after nephrectomy. An injection of renin then would increase mean arterial pressure by 40–100 mm Hg within 2–3 minutes, with a slow decline to baseline over the next 60–90 minutes, whereas, in the sham-nephrectomized animal, a dose of approximately twice this amount of renin resulted in a slightly lesser peak in mean arterial pressure (at 2 minutes), followed by a rapid decline to basal levels within 15–20 minutes.

Dose-Response Curves to Angiotensin I Infusion

Since a changed threshold and/or sensitivity to angiotensin could explain the observed reduction in the rate of blood pressure decline after renin injection in the nephrectomized animal, angiotensin I dose-response curves were determined for both nephrectomized and sham-nephrectomized rats. The results showed a lower threshold of effect and a less steep dose-response slope in the nephrectomized rat. Both of these factors favored a prolongation of the blood pressure response to renin after nephrectomy for any given renin clearance rate, and the data in Figure 2 are plotted in descending order of angiotensin dose of the abscissa to emphasize this point.

![Figure 1](http://circres.ahajournals.org/)

**Figure 1** The time course of mean arterial pressure fall (%) after the maximum response (at 2 minutes) to a renin injection in 22-hour-nephrectomized (Nx) and sham-nephrectomized (Sham-Nx) rats. Mean ± SEM.
"Effective" Plasma Renin Clearance

This was an indirect estimate of the relative rate at which renin disappeared from the circulation after renin injection, based on the decline in mean arterial pressure following a renin injection, and the dose-response curve to angiotensin I in the same rat (see Methods). It takes into account any change in angiotensin I dose-response, so that if a change in the latter were the sole reason for the prolongation of the blood pressure response to renin after nephrectomy, no change in the rate of this "effective renin clearance" would be seen. However, the data (Fig. 3) show a distinct separation of "effective renin clearance" between the nephrectomized and sham-nephrectomized rat experiments, indicating that another factor is involved, most probably a true difference in renin clearance. This point then was investigated directly.

Plasma Renin Disappearance after Intravenous Injections of Rat Renin

The data in Figure 4 show that this was delayed to a varying extent in the nephrectomized rat. However, because of the uncertain (and probably variable) effect of the declining blood pressure on endogenous renin after injection, there was some doubt about the plasma renin levels due to the injection itself, particularly during the latter phases of the renin decay curve. This made interpretation difficult, and therefore, further clearance studies were performed using renin infusions, during which, to judge from the effect of similar elevations in blood pressure with angiotensin I (Fig. 8), the endogenous plasma renin probably was suppressed to less than 10% of the infusion level.
Plasma Renin Clearance Calculated from Renin Infusions

The effect of blood loss per se on endogenous renin first was investigated. So long as the total amount of blood sampling over the 1-hour experimental period was less than 1.2 ml, there was no observed stimulation of endogenous renin. In all subsequent experiments therefore, the volume of each blood sample was kept to 0.2-0.25 ml and the total blood loss for each experiment to less than 1.25 ml.

Rat renin was infused over 30-50 minutes in 15- to 27-hour nephrectomized rats or sham-nephrectomized controls, with two blood samples being taken 10 minutes apart over the last 15 minutes of infusion. Renin concentration reached a plateau within this time, and so these two values were averaged for the calculation of renin clearance. In each experiment, 1-2 further blood samples were taken during the 1st hour after stopping the renin infusion. Figure 5 shows the data obtained during and after infusions of standard rat renin at a dilution of 1/13 and a rate of 0.05 ml/min. The plateau level during infusion in the nephrectomized rat is seen to be approximately twice that in the sham-nephrectomized control group, consistent with a reduction of renin clearance by approximately 50%. This finding is confirmed by the much slower rate of disappearance of renin from the circulation after stopping the infusion in the nephrectomized group (Fig. 5). Experiments were done and assayed in pairs, and the results were expressed as the ratio of renin clearance in the nephrectomized rat to that in its paired sham-nephrectomized control. The data are shown in Table 1 where the reduction of 50% in the renin clearance, 22 hours after nephrectomy, is confirmed. Table 1 also shows that this reduction in renin clearance is independent of the rate of renin infusion and, therefore, of the blood pressure response. This was an important consideration since the mean arterial pressure response to any given level of renin infusion was much greater in the nephrectomized rat.

Table 1 Ratio of Renin Clearance in 22-Hr-Nephrectomized Rats to that in 22-Hr-Sham-Nephrectomized Paired Controls

<table>
<thead>
<tr>
<th>Renin infusion</th>
<th>Renin clearance in 22-hr Nx</th>
<th>Renin clearance in 22-hr Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SEM</td>
</tr>
<tr>
<td>Full strength in Nx</td>
<td>0.51</td>
<td>0.04</td>
</tr>
<tr>
<td>Full strength in Sham</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half strength in Nx</td>
<td>0.48</td>
<td>0.05</td>
</tr>
<tr>
<td>Half strength in Sham</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined results</td>
<td>0.50</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Δ B.P. during infusion in Nx (mm Hg) 78 6 7 70 9 5 74 5 12 0.025

Δ B.P. during infusion in Sham (mm Hg) 54 6 7 67 9 5 59 5 12 0.025

Nx = nephrectomized rats; sham = sham-nephrectomized rats. NS = not significant.
* Paired experiments.

Figure 6 shows the data on the percent fall in renin concentration after stopping renin infusions of varying dilutions and, again, confirms that the slower disappearance rate in the nephrectomized rat is independent of the rate of the infusion, and therefore of the blood pressure responses. Figure 7 adds further evidence by showing that a gross blunting of the blood pressure response to renin injections by prior passive immunization of the rat with...
1 ml of angiotensin II antibody caused very little change in the observed difference in renin decay rate between nephrectomized and sham-nephrectomized rats.

In absolute terms, the renin clearance rate for 22-hour nephrectomized rats was 2.7 ± 0.24 (mean ± SEM) ml/kg per min (n = 5), and this was significantly less (P < 0.001) than the value in 22-hour postsham-nephrectomy controls, where the mean clearance rate was 5.1 ± 0.25 ml/kg per min (n = 15). It will be noted that any clearance ratio calculated between these data would be slightly different from that shown in Table 1, but it is probably less accurate, since it is based on nonpaired data and on fewer numbers in the nephrectomy group.

The Acute Effect of Nephrectomy on Renin Clearance

Because of the relatively slow development of the prolonged pressor response to renin during the 1st 24 hours after nephrectomy, it seemed unlikely that any immediate reduction in renin clearance could explain the whole effect. However, bearing in mind the slow development of the change in the Angiotensin dose-response curve after nephrectomy, it seemed important to investigate this point further and to determine whether any of this altered renin clearance was due to the removal of the kidney per se.

To minimize trauma associated with acute nephrectomy, rats were prepared for these experiments by sham nephrectomy through loin incisions with dissection of the renal pedicles 22 hours before the experiment proper. Renin was then infused and blood taken 30 and 40 minutes later to estimate renin clearance as described above, following which the loin sutures were removed, and the renal pedicles were tied securely. Renin infusion was continued throughout, with blood samples being taken 40–50 minutes later for an immediate postnephrectomy estimates of renin clearance.

Figure 8 shows that when angiotensin I was infused at levels which mimicked the blood pressure increase seen with renin infusions, the endogenous plasma renin concentration was suppressed throughout the experiment.

Table 2 shows the fractional change in renin clearance (post/preoperative) in relation to acute nephrectomy or sham nephrectomy in 10 paired experiments. Some postoperative decreases in renin clearance occurred in the sham-nephrectomized group, particularly when blood loss was associated with the renal pedicle dissection. Significantly
greater decreases were seen following nephrectomy ($P < 0.001$). This difference could not be related to any postnephrectomy fall in endogenous renin, since in calculating the renin clearance immediately preoperatively it was assumed that the endogenous renin had been totally suppressed by the renin infusion, and this would tend to minimize any real difference between the groups. Overall, a significant fall of 26% in renin clearance was observed immediately after acute nephrectomy, in comparison with sham nephrectomy.

Renal Arteriovenous Renin Differences

In these experiments, renin was infused intravenously in normal rats with a left renal venous cannula in situ, and simultaneous arterial and renal venous samples were taken at both 35 and 45 minutes after the commencement of the infusion. Since relatively small arteriovenous renin differences were anticipated, duplicate assays were performed on each of two duplicate incubations from each plasma sample, both arterial and renal venous. These studies were performed to determine whether the observed acute change in renin clearance after nephrectomy was due to a direct effect of the kidney in removing renin from the circulation.

In 16 experiments, the ratio of the renal venous renin to that in simultaneously drawn arterial blood was $0.90 \pm 0.03$, $P < 0.0025$. This ratio was independent of the use of pentolinium tartrate (see Methods) and was $0.90 \pm 0.04$ ($n = 9$) in its presence and $0.89 \pm 0.04$ ($n = 7$) in its absence ($P = 0.45$). In two control experiments in which the venous cannula had entered a lumbar vein below the origin of both renal veins, the venous-to-arterial ratio was 0.99 and 1.01. In two other experiments in which the cannula tip was in the inferior vena cava just above the diaphragm, the corresponding ratios were 0.67 and 0.75, probably reflecting the known hepatic extraction of renin (Heacox et al., 1967).

Renal plasma flow, measured simultaneously in 10 of these experiments, gave a value of $21.0 \pm 2.3$ ml/kg per min. Knowing renal plasma flow and renal arteriovenous renin differences, I could calculate the renin clearance across both kidneys combined. This was $1.63 \pm 0.40$ ml/kg body weight per min ($P < 0.005$).

Effect of Acidification on Plasma Renin Concentration in Rat Plasma Taken during Renin Infusion

Results of a preliminary study in three nephrectomized rats and three sham-nephrectomized controls were variable, and neither a consistent effect nor a consistent difference between the two groups was observed. This point was not pursued since relatively large amounts of blood (up to 2 ml) had to be drawn from each rat for these studies, and it was believed that this might adversely influence the result. More accurate studies will require development of activation methods which can be applied to very small quantities of plasma.

<table>
<thead>
<tr>
<th>Table 2 Fractional Change in Renin Clearance in Relation to Acute Nephrectomy or Sham-Nephrectomy in 10 Paired Experiments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Renin clearance</td>
</tr>
<tr>
<td>Ratio postop</td>
</tr>
<tr>
<td>preop</td>
</tr>
<tr>
<td>0.84*</td>
</tr>
<tr>
<td>0.56*</td>
</tr>
<tr>
<td>0.90</td>
</tr>
<tr>
<td>0.98</td>
</tr>
<tr>
<td>0.97</td>
</tr>
<tr>
<td>0.81</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>SEM</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>P</td>
</tr>
</tbody>
</table>

* Some blood loss after operation.
Discussion

The reason for the development of the prolonged pressor response to renin after nephrectomy has remained obscure since its original description by Tigerstedt and Bergman (1898). Studies by Bing and Nielson (1973) on the effect of the angiotensin blocker "saralasin" leave little doubt that it is angiotensin mediated, but beyond this, very little is established.

Data on renin clearance after nephrectomy are conflicting. In the dog, Houssay et al. (1942) found that the time of disappearance of renin from the blood increased from less than 30 minutes to approximately 1 hour in animals recently nephrectomized (3-4 hours) and to 2.5 hours in 48-hour-nephrectomized animals. Assaykeen and colleagues (1968) found that the clearance of injected renin in 4-hour-nephrectomized dogs was similar to that calculated for endogenous renin immediately following nephrectomy. Values measured in the latter situation by Michelakis and Mizukoshi (1971) were comparable, with a half-time of 13 minutes for the fast component and 93 minutes for the second slower component. Schneider et al. (1968) observed a similar two-component disappearance of renin in somatographically shorter half-lives in the 4-hour bilaterally nephrectomized dog.

In bilaterally nephrectomized rats, Schaechtelin et al. (1964) found that the prolonged pressor response to injected renin 20 hours after nephrectomy was not associated with a prolonged persistence of renin in the blood, from which it disappeared within 1 hour. However, these workers used an indirect in vivo renin bioassay. The more precise studies of Peters-Haefeli (1971) show a reduction in plasma renin clearance from 2.9 ml/kg per min before nephrectomy to 1.6 ml/kg per min 2 hours after total nephrectomy in the rat, but the situation at a later stage after nephrectomy was not investigated.

The present study has confirmed the development of a prolonged pressor response to renin over the 24-hour period following nephrectomy and has defined the involvement of at least two factors in its cause. First, the blood pressure dose-response to angiotensin I is changed at the 22-hour point after nephrectomy with a decrease in threshold effect and a decrease in slope, both factors tending to prolong blood pressure decline from any given point, even assuming a similar renin clearance rate after nephrectomy. However, this factor alone was not sufficient to account for the whole effect, and further investigation showed that renin clearance was reduced to 50% in the 22-hour-nephrectomized rat.

Because the blood pressure response to renin is not obviously prolonged during the first 1-hour postnephrectomy, it seemed unlikely that this reduction in renin clearance would be an immediate effect of the nephrectomy per se. However, since it was possible that the gradual onset of the prolonged response was due to an immediate reduction in renin clearance, together with a slowly developing change in the angiotensin dose-response curve, further studies were carried out on the immediate effect of nephrectomy on renin clearance. These studies indeed did show a reduction in renin clearance at this point by an average value of 25%. Thus, not unlike the findings of Houssay et al. (1942), there is a reduction in renin clearance immediately after nephrectomy (by 25%) and a further reduction (to 50%) during the next 24-hour period.

Direct measurements of the renal clearance of renin were obtained for measurements of simultaneous renal plasma flow and renal arteriovenous renin difference. These showed a significant clearance of renin across the kidney, representing approximately 10% of renal plasma flow.

The role and origin of the recently described inactive forms of renin are uncertain. (Morris and Lumbers, 1972; Boyd, 1974; Day et al., 1975) are uncertain. Recent data (Derkx, 1976; Boyd, 1977) suggest that they may come from the kidney as secretion forms of the enzyme, but the possibility still exists that they may be renal clearance forms, and an examination of this was undertaken in the present study. However, preliminary experiments showed a variable and inconsistent effect of activation by acidification, and since it was felt that the relatively large amounts of blood drawn for these studies may have complicated the result by stimulating endogenous renin release in the sham-nephrectomized group, further studies were postponed pending the development of methods for renin activation in smaller quantities of plasma.

Acknowledgments

I am indebted to Jenny Owen and Glen Tobias for skilled technical assistance.

References


Boyd GW, Peart WS (1968) Production of high-titre antibody against free angiotensin II. Lancet 2: 129-133


Pulmonary Vasodilator Activity of Prostacyclin (PGI2) in the Cat

ALBERT L. HYMAN AND PHILIP J. KADOWITZ

SUMMARY We studied the pulmonary vascular effects of prostacyclin, PGI2, in the cat with intact chest under conditions of controlled blood flow. Intralobar injections of PGI2, 0.03–1 µg, decreased arterial pressure in the perfused lobe in a dose-dependent manner. Inasmuch as lobar blood flow was held constant and left atrial pressure was unchanged, the fall in lobar arterial pressure reflects a decrease in lobar vascular resistance. Prostaglandin E1 (PGE1) and nitroglycerin also decreased lobar arterial pressure; however, PGI2 had greater vasodilator activity than did these substances. Vasodilator responses to PGI2, PGE1, and nitroglycerin in absolute terms were dependent on the baseline level of tone in the pulmonary vascular bed. Prostacyclin reversed the hypertensive and platelet aggregating effects of ADP in the lobar vascular bed. These data indicate that PGI2 has significant vasodilator activity in the feline pulmonary lobar vascular bed.

IN the lung, arachidonic acid is transformed into the cyclic endoperoxide intermediates, PGG2 and PGH2, by a microsomal cyclooxygenase (Nugteren and Hazlehof, 1973; Hamberg and Samuelsson, 1974). The endoperoxide intermediates then are converted by specific terminal enzymes into prostaglandins (PG), thromboxane A2, and a newly discovered bicyclic prostaglandin, prostacyclin, or PGI2 (Nugteren and Hazlehof, 1973; Hamberg and Samuelsson, 1974; Gryglewski et al., 1976). PGI2 is the major metabolic product formed from arachidonic acid and endoperoxide intermediates in vascular tissue and, since PGI2 is a potent inhibitor of platelet aggregation, it has been postulated that it may serve to protect vessel endothelium from the adverse effects of intravascular platelet aggregation and thrombus formation (Bunting et al., 1976; Gryglewski et al., 1976; Dusting et al., 1977). PGI2 relaxes strips of mesenteric and celiac arteries but not strips from aorta and vena cava (Bunting et al., 1976). Prostacyclin decreases systemic arterial pressure in all species in which it has been studied, and a PGI2 analog has been shown to have marked vasodilator activity in the feline pulmonary lobar and mesenteric vascular beds (Hyman et al., 1977; Paustian et al., 1977; Armstrong et al., 1978; Fitzpatrick et al., 1978, Lefer et al., 1978). Although PGI2 is formed in blood vessels, “PGI2-like” substances are released from the lung, and the metabolite, 6-keto-PGF1α, is released from the lung after immunological challenge, the direct effects of PGI2 in the pulmonary vascular bed are uncertain (Dawson et al., 1976; Gryglewski et al., 1976; Gryglewski et al., 1978). In a recent study in the anesthetized dog, PGI2, in a dose of 0.5 µg/kg, iv, caused a 1.4% decrease in pulmonary arterial pressure (Fitzpatrick et al., 1978). However, in that study in the open-chest dog, the effects of PGI2 on cardiac output and left atrial pressure were not assessed. In another recent study, PGI2 has been shown to decrease pulmonary arterial pressure in the dog; however, cardiac output was changed (Kadowitz et al., 1978).
The prolonged pressor response to renin in the nephrectomized rat.

G W Boyd

Circ Res. 1979;45:396-404
doi: 10.1161/01.RES.45.3.396

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1979 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/45/3/396

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/