In Vivo Influence of Prostaglandin I₂ on Systemic and Renal Circulation in the Rat
Toshimasa Yoshioka, Aida Yared, Hirofumi Miyazawa, and Iekuni Ichikawa

SUMMARY The effect of prostaglandin I₂ and two other vasodilator agents, acetylcholine and sodium nitroprusside, on systemic and renal circulation was studied in 29 adult euvolemic Sprague-Dawley rats. Intra-aortic infusion of prostaglandin I₂ (3.6 µg/kg/hr; n = 6 rats) produced significant vasodilation (p < 0.05), as indicated by an average reduction in total peripheral vascular resistance of 24.8 ± 2.0%, while renal vascular resistance remained essentially unchanged. Essentially identical findings were obtained in a separate group of six rats pretreated with intravenous administration of saralasin (0.5 mg/kg/hr). In contrast, in another group of six rats pretreated with saralasin, intra-aortic infusion of acetylcholine (0.35 mg/kg/hr), which caused a reduction in total peripheral vascular resistance (21.4 ± 3.8%) comparable to that induced by prostaglandin I₂, produced a significant fall in renal vascular resistance (average, 27.7 ± 5.0%) and, hence, an increase in renal blood flow (average, 26.2 ± 2.9%). The effect of sodium nitroprusside (0.4 mg/kg/hr i.v.) was intermediate between those of prostaglandin I₂ and acetylcholine: both renal vascular resistance and total peripheral vascular resistance fell mildly. These results indicate that prostaglandin I₂, given in a dose sufficient to cause systemic vasodilation, fails to induce any discernible renal vasodilator response and that this absence of renal vasodilation by prostaglandin I₂ in vivo is not due, as previously postulated, to the highly efficient offsetting influence of intrarenal angiotensin II release.

Key Words • acetylcholine • nitroprusside • vasodilator • microsphere • renal vascular resistance • angiotensin II

Prostaglandins are now well recognized as important modulators of renal hemodynamics. Of interest, although many prostaglandins, including prostaglandin I₂ (PGI₂), cause a profound dilative response in a variety of systems, PGI₂ given in vivo has been shown not to elicit renal vasodilation in some animal species, such as the rat. Since PGI₂ is capable of stimulating renal renin and angiotensin II release, the intrarenal PGI₂-sensitive production of angiotensin II was invoked to account for the absence of renal vasodilator effect of PGI₂. Such a release of endogenous angiotensin II, however, may not necessarily be unique to PGI₂, since other vasodilators are also potentially capable of inducing angiotensin II release through their depressor influence on systemic (hence, renal) perfusion pressure.

The present study was designed 1) to investigate the role of angiotensin II in determining renal hemodynamic pattern during in vivo administration of PGI₂ and 2) to study the direct renal vascular effect of PGI₂ and other vasodilators during pharmacological blockade of angiotensin II action.

Materials and Methods
Studies were performed in 29 adult Sprague-Dawley rats (weight, 228-378 g) that were allowed free access to regular rat chow and tap water until the time of study. Animals were anesthetized by intraperitoneal injection of thiobutabarbital (Inactin), 100 mg/kg (BYK Gulden Konstantz, W. Germany), and placed on a temperature-regulated table. Following tracheostomy, indwelling polyethylene catheters (PE-50, Clay Adams, Parsippany, NJ, USA) were placed into the left and right jugular veins for subsequent infusion of plasma and test agents and into the left femoral artery.
for monitoring mean arterial pressure (MAP) and heart rate (HR) and for periodic blood collection. The MAP and HR were measured by an electronic transducer (Model p23Db; Gould, Inc., Cleveland, OH, USA) connected to a direct-writing recorder (Model 2200S; Gould). The left femoral vein was catheterized for whole blood transfusion (described in a later section). Subsequently, catheterization of the left ventricle was performed through the right carotid artery; correct placement of the catheter tip was confirmed by obtaining a typical left ventricular pressure pattern. Laparotomy was then performed. A segment (approximately 5 mm long) of the left renal artery was freed from the adjacent renal vein and surrounding adventitia, and an electromagnetic flow probe (2 mm in circumference, EP102; Carolina Medical Electronics, King, NC, USA) was placed around it to monitor the whole kidney blood flow rate (renal blood flow, RBF). A 30-gauge needle was inserted into the abdominal aorta just above the origin of the left renal artery, and an infusion of 0.9% NaCl solution was started at a rate of 1.2 ml/hr. To maintain the circulating plasma volume at normal euvoletic level during the experiment, each rat received isooncotic rat plasma in a volume of 10 ml/kg i.v. over 20 to 30 minutes followed by continuous infusion at the rate of 0.6 ml/kg/hr.  

Experimental Groups

Group 1 (n = 6, time control) rats received a continuous intravenous infusion of indomethacin (2 mg/kg/hr; Sigma Chemical Co., St. Louis, MO, USA) throughout the study.  

Approximately 20 minutes after completion of surgical preparation, when MAP, HR, and RBF reached steady state levels, cardiac output (CO) was measured. Twenty minutes later, while MAP, HR, and RBF were still being monitored, the CO measurement was repeated.  

In Group 2A (n = 6) rats, the first period of the study identical to that described for Group 1. At the completion of initial CO measurement, intra-aortic infusion of PGI (Sigma) in Tris buffer (Sigma), pH 8.5, diluted 10-fold in normal saline was started at the rate of 3.6 μg/kg/hr (0.18 ml/hr). This dose of PGI was determined to produce a mild systemic vasodilation; the doses of the other vasodilators were selected to produce a comparable degree of systemic vasodilation. Approximately 20 minutes later, when MAP, HR, and RBF reached new steady levels, CO measurement was repeated.  

Experiments in Group 2B (n = 6) rats were performed in the same fashion as in Group 2A except that Group 2B received, in addition to indomethacin, a continuous infusion of saralasin (0.5 mg/kg/hr; Norwich-Eaton Pharmaceuticals, Norwich, NY, USA).  

In Group 3 (n = 6) rats, the initial measurement of CO was performed while infusing saralasin in the same manner as in Group 2B. Then, intra-aortic infusion of acetylcholine chloride (Sigma) was started at a rate of 0.35 mg/kg/hr (1.2 ml/hr), and CO measurement was repeated.  

In Group 4 (n = 5) rats, the initial measurement of CO was performed while infusing saralasin in the same manner as in Group 2A. Then, intravenous infusion of sodium nitroprusside (Abbott Laboratories, North Chicago, IL, USA) was started at a rate of 0.40 mg/kg/hr. When MAP, HR, and RBF reached new steady levels, a second measurement of CO was performed.  

Measurements of Cardiac Output and Renal Blood Flow

The standard radioactive microsphere technique for regional blood flow measurement was adapted for estimation of CO, as described by Hoffbrand and Forsyth and McDevitt and Nies. Carbonized plastic microspheres, 15 ± 3 (mean ± SD) μm in diameter, labeled with 51Cr (Tracer microspheres, 3M, St. Paul, MN, USA) were used for the study. Before the study, 50 μl of an isotonic saline solution containing approximately 35,000 particles was placed into an 8-cm length of Silastic tubing (inside diameter, 0.05 in; Dow Chemical Co., Midland, MI, USA). The tubing was capped at both ends to prevent evaporation, and its radioactivity was measured immediately before use in an automated gamma counter (Gamma Trac 1191, TM Analytic, Elk Grove Village, IL, USA). At the time of study, this microsphere suspension was disaggregated by sonication, injected into the left ventricular cavity, and flushed with 0.6 ml of normal saline solution over a period of 0.2 minute. Starting immediately before, and ending immediately after, completion of the microsphere injection, a timed arterial blood sample was collected by unclamping the femoral arterial catheter into a previously weighed, graduated test tube. To maintain venous return, the blood being lost (≈1.8 ml) was replaced, volume to volume, through the femoral venous catheter, using whole blood obtained from littermates of the experimental animals. The volume of the blood collected was derived from the change in weight of the graduated test tube, divided by the specific gravity of blood (0.94), and its radioactivity was measured. Residual radioactivity in the Silastic tubing and its caps was also measured. The CO was calculated as (count injected × reference sample withdrawal rate)/reference sample count.  

It has been shown previously and confirmed by us in the present study that repeated injections of 15-μm microspheres do not affect systemic hemodynamics when the cumulative number of microspheres injected is less than 100,000.  

Renal blood flow was measured by placing a 2-mm (circumference) electromagnetic flow probe (EP 102; Carolina Medical Electronics, King, NC, USA) around the left renal artery, which was connected to a square-wave electromagnetic flowmeter (Model 501; Carolina Medical Electronics). This flowmeter system was calibrated in vivo before use.  

Calculations and Statistical Analysis

The following parameters were derived from MAP, RBF, and CO: total peripheral vascular resistance (TPVR) = MAP (in millimeters of mercury)/CO (in milliliters per minute), renal vascular resistance (RVR) = MAP (in millimeters of mercury)/RBF (in milliliters per minute), and RVR/TPVR ratio. Results
were analyzed statistically by using paired and unpaired \( t \) test. Values are expressed as means \( \pm 1 \) SE.

**Results**

The results obtained for studies using Groups 1 through 4 during the two experimental periods are summarized in Table 1. The changes in the various parameters from the first to the second study period in the five groups are shown in Figure 1.

In Group 1 (control animals receiving only indomethacin), no significant change was seen between the initial and second period in any of the systemic or renal hemodynamic parameters under study. Thus, MAP, HR, CO, RBF, TPVR, RVR, and RVR/TPVR remained essentially constant. In Group 2A (indomethacin-treated animals), a mild reduction in MAP was uniformly seen following infusion of PGI\(_2\) (average, from 115 ± 9 mm Hg to 108 ± 7 mm Hg; \( p < 0.05 \)). Since CO increased significantly (average, from 89 ± 11 ml/min to 107 ± 14 ml/min; \( p < 0.005 \)), this reduction in MAP during PGI\(_2\) infusion reflected a fall in TPVR (average, from 1.5 ± 0.1 mm Hg • min • ml\(^{-1}\) to 1.0 ± 0.1 mm Hg • min • ml\(^{-1}\); \( p < 0.001 \)). In contrast to these changes in TPVR and CO, RVR and RBF remained essentially unchanged.

Consequently, the value for RVR/TPVR increased substantially during PGI\(_2\) infusion (from 10.0 ± 0.5 to 12.5 ± 0.8; \( p < 0.05 \)), which indicates a more pronounced vasodilator effect of PGI\(_2\), in the dose given, on extrarenal than renal vasculature.

In Group 2B (animals receiving saralasin and indomethacin), the changes in the various hemodynamic parameters during infusion of PGI\(_2\) followed a pattern similar to that observed in Group 2A non-saralasin-treated animals (Table 1). Thus, there was a mild but significant reduction in MAP (from 117 ± 8 mm Hg to 108 ± 7 mm Hg; \( p < 0.001 \)), in association with a significant increase in CO (from 104 ± 7 ml/min to 123 ± 8 ml/min; \( p < 0.005 \)). Again, RVR and RBF remained constant, so that RVR/TPVR increased remarkably (average, from 8.7 ± 1.1 to 12.4 ± 2.3; \( p < 0.005 \)). This reduction in RVR was greater than the increase in TPVR, as indicated by a slight but significant fall in RVR/TPVR (from 10.3 ± 1.4 to 9.8 ± 1.5; \( p < 0.005 \)). This potent renal vasodilative effect of acetylcholine led to a rise in RBF (from 10.3 ± 1.1 ml/min to 13.0 ± 1.2 ml/min; \( p < 0.001 \)) during the second study period.

The pattern of the changes seen following nitroprusside infusion in Group 4 was intermediate between those observed in Group 2B and Group 3 (Table 1). A mild reduction in MAP was seen (from 104 ± 5 mm Hg to 93 ± 2 mm Hg; \( p < 0.05 \)) in association with a mild fall in TPVR (from 11.0 ± 1 mm Hg • min • ml\(^{-1}\) to 9.0 ± 0.1 mm Hg • min • ml\(^{-1}\); \( p < 0.005 \)), while CO increased slightly but not significantly. The reduction in TPVR was accompanied by a mild but significant reduction in RVR (from 13.9 ± 1.1 mm Hg • min • ml\(^{-1}\) to 13.0 ± 1.0 mm Hg • min • ml\(^{-1}\); \( p < 0.05 \)), so that both RVR/TPVR and RBF were essentially unaffected.

**Discussion**

Prostaglandins, products of arachidonic acid metabolism by the cyclooxygenase pathway, have been known to modulate the renal circulatory dynamics under a variety of physiological and pathophysiological circumstances. Studies on the dog have shown that prostaglandin E\(_2\), prostaglandin D\(_2\), and PGI\(_2\) reduce renal vascular resistance. In rats, however, unresponsiveness of the renal vasculature to PGI\(_2\) has been reported in a study of whole kidney measurement, and an increase in renal microvascular resistance has been reported in a recent micropuncture study.

In the present study, we examined simultaneously the systemic and renal vascular effects of PGI\(_2\) in the rat. When PGI\(_2\) was administered intra-aortically just above the origin of the left renal artery, TPVR decreased substantially along with a significant increase in cardiac output, whereas no significant changes occurred in the renal hemodynamic parameters. This differential effect of PGI\(_2\) on extrarenal versus renal vasculature was evidenced by an increase in RVR/TPVR, which confirmed the previously reported insensitivity of the renal vasculature to PGI\(_2\).

Since a fall in MAP is expected to lead to some degree of reduction in renal vascular resistance through the renal autoregulatory response, our finding of an essentially unchanged value of RVR during exogenous PGI\(_2\) administration even more strongly suggests weakness of a direct renal vasodilator influence of PGI\(_2\) at the given dose.

The uniqueness of PGI\(_2\) action becomes more evident when compared with that of other vasodilators. Figure 1 depicts the changes in the absolute values of TPVR and RVR as well as in the RVR/TPVR ratio. Acetylcholine, given in a fashion similar to PGI\(_2\),
caused a reduction in TPVR of a magnitude comparable to that induced by PGI₂; however, it led to a marked decrease in RVR, which contrasted to the near constancy in RVR during PGI₂ infusion (Figure 1). Nitroprusside given intravenously produced a reduction in TPVR, which again was comparable to that of PGI₂. Its effect on renal hemodynamics was intermediate between those of PGI₂ and acetylcholine (Figure 1). In this regard, previous in vivo¹²⁻¹⁴ and in vitro¹⁵ studies have shown that PGI₂, given in doses higher than in the present study led to a reduction in renal vascular resistance. It seems likely, therefore, that when a high local level is achieved, the renal vasodilator effect of PGI₂ is observed.

Since some of the prostaglandins, including PGI₂, stimulate renin in intact animals⁴ as well as in preparations of isolated glomeruli,⁵ it has previously been postulated that the absence of a renal dilator action of low dose PGI₂, as we used, is secondary to a PGI₂-induced increase in the level of intrarenal angiotensin II, which blunts the direct renal vasodilator effect of PGI₂. This hypothesis seemed supported, at the level of the single nephron, by the recent micropuncture study of Schor and Brenner.³ These authors measured the glomerular microcirculatory parameters of superficial nephrons in Munich-Wistar rats. In rats receiving PGI₂ intra-aortically, the glomerular plasma flow rate of superficial nephrons was reported to be significantly lower than that in control animals, saralasin administration in those PGI₂-treated animals led to a marked increase in single nephron glomerular plasma flow rate, to a level some 50% higher than that of control rats.

TABLE 1. Summary of Hemodynamic Parameters of the Study

<table>
<thead>
<tr>
<th>Group</th>
<th>MAP  (mm Hg)</th>
<th>HR  (beats/min)</th>
<th>CO  (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>115 ± 7</td>
<td>316 ± 7</td>
<td>113 ± 27</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>116 ± 5</td>
<td>316 ± 5</td>
<td>112 ± 25</td>
</tr>
<tr>
<td>2A (n = 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>115 ± 9</td>
<td>292 ± 15</td>
<td>89 ± 11</td>
</tr>
<tr>
<td>Indomethacin + PGI₂</td>
<td>108 ± 7*§</td>
<td>296 ± 13</td>
<td>107 ± 14§</td>
</tr>
<tr>
<td>2B (n = 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indomethacin + saralasin</td>
<td>117 ± 8</td>
<td>366 ± 19</td>
<td>104 ± 7</td>
</tr>
<tr>
<td>Indomethacin + saralasin + PGI₂</td>
<td>108 ± 7†</td>
<td>352 ± 19</td>
<td>123 ± 8*</td>
</tr>
<tr>
<td>3 (n = 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saralasin</td>
<td>114 ± 5</td>
<td>278 ± 14</td>
<td>100 ± 9</td>
</tr>
<tr>
<td>Saralasin + acetylcholine</td>
<td>103 ± 4‡</td>
<td>292 ± 12+</td>
<td>116 ± 9†</td>
</tr>
<tr>
<td>4 (n = 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saralasin</td>
<td>104 ± 5</td>
<td>391 ± 11</td>
<td>103 ± 11</td>
</tr>
<tr>
<td>Saralasin + nitroprusside</td>
<td>93 ± 2*</td>
<td>408 ± 111†‡‡</td>
<td>113 ± 9</td>
</tr>
</tbody>
</table>

Values are expressed as means ± 1 SE. No significant difference was noted between the changes in Groups 2A and 2B (p > 0.05).

MAP = mean arterial pressure; HR = heart rate; CO = cardiac output; RBF = renal blood flow; TPVR = total peripheral vascular resistance; RVR = renal vascular resistance.

* p < 0.05, †p < 0.005, ‡p < 0.001, significant changes from the first to the second study period.

§p < 0.001, ††p < 0.025, ‡‡p < 0.001, significant changes from the first to the second study period. Changes are significantly different between Groups 1 and 2A.

**p < 0.005, ††p < 0.05, ‡‡p < 0.001, changes are significantly different between Groups 2B and 3.

†††p < 0.005, changes are significantly different between Groups 2B and 4.
Since an enhanced release of angiotensin II during PGI2 administration in intact animals could be triggered by its systemic vasodilator action, our experimental protocols were designed to test the possibility that attenuation (caused by secondary angiotensin II release) of a drug's renal dilator effect might also occur during administration of other vasodilators. We obtained no evidence that the simultaneous administration of an angiotensin inhibitor potentiated the renal dilator influence of PGI2. Rather, as shown in Figure 1, both RVR and RVR/TPVR tended to increase with saralasin treatment. No obvious explanation is available for this discrepancy between the results of Schor and Brenner and ours, since the dose and route of administration of PGI2, indomethacin, and saralasin were the same in both studies. It could be related in part to the fact that they studied the dynamics of superficial nephrons, while we measured total kidney function; the sensitivity with regard to the direct vasodilator influence and the angiotensin-releasing effect of PGI2 may vary between superficial and deep cortical nephrons. A strain difference in the response to PGI2 between Munich-Wistar and Sprague-Dawley rats may also explain this discrepancy.

Our results indicate that the absence of whole kidney vasodilation by PGI2 given in vivo in some species is not necessarily consequent to the opposing constrictive influence of angiotensin II, released in response to the vasodepressor effect of PGI2, but is more likely due to a direct vasodilator action that is less prominent in renal than in extrarenal vasculature.

Acknowledgment
The authors are grateful to Janet Stanley for her expert secretarial assistance.

References

<table>
<thead>
<tr>
<th>Table 1 (continued).</th>
<th>RBF (ml/min)</th>
<th>TPVR (mm Hg · min · ml⁻¹)</th>
<th>RVR (mm Hg · min · ml⁻¹)</th>
<th>RVR/TPVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.5 ± 1.4</td>
<td>1.1 ± 0.1</td>
<td>11.7 ± 1.2</td>
<td>11.6 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>10.4 ± 1.4</td>
<td>1.1 ± 0.1</td>
<td>11.8 ± 1.2</td>
<td>11.7 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>8.3 ± 1.4</td>
<td>1.5 ± 0.1</td>
<td>15.1 ± 1.7</td>
<td>10.0 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>8.7 ± 1.8</td>
<td>1.0 ± 0.1†</td>
<td>14.1 ± 2.1</td>
<td>12.5 ± 0.8*‡</td>
<td></td>
</tr>
<tr>
<td>11.4 ± 2.3</td>
<td>1.2 ± 0.1</td>
<td>10.6 ± 2.0</td>
<td>8.7 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>11.2 ± 2.4</td>
<td>0.9 ± 0.1†</td>
<td>10.7 ± 2.4</td>
<td>12.4 ± 2.3*</td>
<td></td>
</tr>
<tr>
<td>10.3 ± 1.1</td>
<td>1.1 ± 0.1</td>
<td>11.9 ± 1.5</td>
<td>10.3 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>13.0 ± 1.2†**</td>
<td>0.9 ± 0.1†</td>
<td>8.6 ± 1.0†‡</td>
<td>9.8 ± 1.5†**</td>
<td></td>
</tr>
<tr>
<td>7.6 ± 0.5</td>
<td>1.1 ± 0.1</td>
<td>13.9 ± 1.1</td>
<td>13.6 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>7.3 ± 0.6</td>
<td>0.9 ± 0.1†</td>
<td>13.0 ± 1.0*</td>
<td>15.7 ± 1.4</td>
<td></td>
</tr>
</tbody>
</table>


In vivo influence of prostaglandin I2 on systemic and renal circulation in the rat.
T Yoshioka, A Yared, H Miyazawa and I Ichikawa

Hypertension. 1985;7:867-872
doi: 10.1161/01.HYP.7.6.867

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1985 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/7/6_Pt_1/867

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension 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 Hypertension is online at: http://hyper.ahajournals.org//subscriptions/