Angiotensin II mediates systemic rebound hypertension after cessation of prostacyclin infusion in sheep

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Robbins, Ivan M., Leslie L. Cuiper, C. Michael Stein, Alastair J. J. Wood, Huaib. He, Richard Parker, and Brian W. Christman. Angiotensin II mediates systemic rebound hypertension after cessation of prostacyclin infusion in sheep. J. Appl. Physiol. 85(2): 731–737, 1998.—Prostacyclin (or epoprostenol), an arachidonic acid metabolite, is an effective treatment for patients with primary pulmonary hypertension. Interruption of chronic prostacyclin infusion can result in recurrent symptoms of dyspnea and fatigue. The etiology of this phenomenon is unknown. We hypothesized that sympathoadrenal activation could lead to increased vascular tone after abrupt termination of the infusion. To evaluate this effect, we monitored six chronically instrumented, awake sheep during and after infusion of prostacyclin. Prostacyclin decreased mean arterial pressure (MAP) by 14% and increased cardiac output by 33%. After the infusion ceased, MAP rebounded 23% above baseline, and cardiac output decreased by 28% from peak values within 10 min. We were unable to demonstrate an increase in norepinephrine levels after cessation of prostacyclin, nor did a-adrenergic blockade affect postinfusion hemodynamics. However, plasma renin activity increased >10-fold at peak infusion and remained elevated for up to 2 h after discontinuation of prostacyclin. Coinfusion of the angiotensin II receptor antagonist L-158,890 resulted in complete abrogation of the postcessation rise in MAP. We conclude that renin-angiotensin system activation is primarily responsible for systemic hypertension occurring after abrupt cessation of prostacyclin infusion in sheep and that angiotensin II receptor blockade prevents this response. Our data do not support a role for sympathetic nervous system activation in the systemic pressor response after prostacyclin infusion.

prostaglandin I2; epoprostenol; pulmonary hypertension; renin; norepinephrine

Prostaglandin I2 (epoprostenol or prostaglandin I2 (PGI2)), an endothelium-derived arachidonic acid metabolite, is a potent vasodilator. It has been used in the treatment of peripheral vascular disease (35, 36), Raynaud's phenomenon (5), and more extensively, primary pulmonary hypertension (PPH) (2, 3, 18, 21, 22, 31). Because of its ability to inhibit platelet aggregation, PGI2 has also been employed during dialysis and with extracorporeal circulation during cardiopulmonary bypass (30, 34). In patients with pulmonary hypertension, a decrease in the major urinary metabolite of PGI2 (2,3-dinor-6-keto-PGF1α), along with an increase in 11-dehydro-TxB2, the urinary metabolite of the primarily platelet-derived vasoconstrictor thromboxane A2 (TxA2) implies that they may have a relative impairment in endothelial production of PGI2 (9).

Chronic infusion of PGI2 for >8 wk in patients with PPH improves symptoms, decreases pulmonary arterial pressure (PAP), and increases cardiac output (CO), leading to a decrease in pulmonary vascular resistance (PVR). Such patients may benefit, even if they are initially unresponsive to or intolerant of other vasodilators (3, 18–22, 31). These advantages have recently been confirmed, and improved survival has been shown, in a prospective, randomized, multicenter trial comparing prostacyclin with conventional therapy (2). Beneficial effects of PGI2 have also been claimed in patients awaiting lung transplantation; some of these patients have received PGI2 for 6 yr (3, 19).

The rapid onset of action and short half-life of ~2–3 min necessitate administration of PGI2 by continuous infusion (11). Most studies evaluating the efficacy of PGI2 in PPH have noted recurrent symptoms of dyspnea or fatigue in up to one-third of patients when their infusions were abruptly discontinued, and one death was reported after PGI2 infusion was inadvertently interrupted (3). In an attempt to elucidate the mechanism responsible for this postinfusion deterioration, we employed a large-animal model and observed a substantial elevation in mean arterial pressure (MAP) and a decrease in CO after acute cessation of PGI2 (10).

Initially, we hypothesized that the hypertensive response after termination of prostacyclin was mediated by platelet activation with subsequent TxA2 production; however, results from our sheep studies did not support this mechanism (10). Several studies have demonstrated that systemic infusion of epinephrine (Epi) for only a few hours results in prolonged hemodynamic alterations, even after circulating concentrations of Epi have returned to baseline. This is thought to be caused by Epi uptake into the synaptic nerve terminal and its subsequent re-release, along with norepinephrine (NE) as a cotransmitter (6, 7, 14, 26). Epi, in turn, stimulates further NE release through presynaptic β2-adrenergic receptor stimulation to both amplify and prolong the sympathetic response (8, 15, 24, 32). Hypotension is a potent stimulus for endogenous Epi release. Therefore, we considered that Epi release, in response to the PGI2-induced decrease in MAP, might contribute to the postinfusion hypertensive response by facilitating NE release. An alternative explanation is that the postinfusion pressor response is due to activation of the renin-angiotensin system (RAS). In support of RAS involvement is the previously documented direct (28) and indirect (16, 27) stimulation of renin release by PGI2. The 20- to 30-min half-life of renin, substantially longer than that of PGI2, could

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account for the prolonged hypertensive response after PGI₂ infusion is stopped. The purpose of this study was
to determine in a sheep model the relative contributions of the sympathoadrenal system and RAS to the
rebound hypertension that follows cessation of PGI₂.

METHODS

Animal preparation and experimental protocol. Yearling sheep (weight 24–35 kg) were managed according to institutional
animal care guidelines, and the protocols were approved by the Animal Care Committee of the Vanderbilt
University School of Medicine. Anesthesia was induced with thiopental sodium (20 mg/kg iv). The sheep were intubated
and mechanically ventilated, and anesthesia was maintained with a mixture of halothane and oxygen. A Silastic catheter
and an 8-Fr introducer (Cordis, Miami, FL) were placed in the common carotid artery and internal jugular vein, respectively,
via a small incision that was made in the right neck under sterile conditions. The incision was closed, and the
animals were allowed to recover for 24–48 h. Additionally, one of the six sheep underwent a left thoracotomy under
sterile conditions. The main pulmonary artery and the left atrium were cannulated with Silastic catheters, and a 20-mm
perivascular probe (Transonic Systems, Ithaca, NY) was placed around the main pulmonary artery to continuously
record CO.

A 7.5-Fr Edwards Swan-Ganz catheter (Baxter Healthcare, Irvine, CA) was positioned through the introducer before the
experiment. Hemodynamic measurements were carried out in awake, upright sheep, with the transducer positioned at
the level of the left atrium. MAP, PAP, and left atrial pressure (LAP) were recorded on a Hewlett-Packard 7788A recorder.
Pulmonary capillary wedge pressure (PCWP) was obtained by balloon occlusion of the pulmonary artery in five sheep,
and the LAP was measured directly in one sheep. CO was determined by the thermodilution technique with icd saline
injectate, averaging two to four measurements at each time point, on a 9520A Cardiac Output Computer (American
Edwards Laboratories, Santa Ana, CA). In the animal with the perivascular probe, CO was measured on a 7101 Ultra-
sonic Blood Flow Meter (Transonic Systems). The measurements obtained were calibrated before each experiment by
comparison with CO obtained by the thermodilution technique.

MAP was recorded as millimeters of mercury, whereas
PAP and LAP were registered as centimeters of water and then converted to millimeters of mercury for calculation of
resistance. PVR is reported in Wood units by using the following standard formulas: PVR = (PAP – PCWP)/CO or
(PAP – PLA)/CO.

The sodium salt of prostacyclin (Filoan) was graciously provided by Glaxo-Wellcome (Research Triangle Park, NC); it
was reconstituted in sterile glycine buffer to give a concentration of 10,000 ng/ml before the experiment. It was shielded
from light to prevent drug inactivation. On the basis of the dose-response relationship determined in prior experiments,
PGI₂ was begun at 100 ng·kg⁻¹·min⁻¹ and titrated to a maximal dose of 500 ng·kg⁻¹·min⁻¹ over 1 h or to a 20%
decrease in MAP. Previous studies showed no additional vasodilatory effect with further increases in dosage (10).
During all experiments, the maximal dose of prostacyclin was maintained for >15 min (6 half-lives) before cessation.

Role of catecholamines. To determine the role of catechol-
amines in the development of rebound hypertension, PGI₂
was infused in six sheep, as described above. On a different
day, a second experiment was performed with each animal. A 5-mg intravenous bolus of the α-adrenergic-antagonist phenen-
tolamine (Winthrop Pharmaceuticals, New York, NY) was administered 5 min before the PGI₂ infusion was stopped.
The drug was given at this time because of a reported half-life of 19.5 min in humans. The dose used was based on previous
studies in sheep that had determined the amount required to return ovine pulmonary and systemic blood pressure to
baseline after preconstriction (30% above baseline) with NE (23).

Calculation of NE spillover. [³H]NE [norepinephrine, [ring-
2,5,6-H]²] (56.9 Ci/mmol; New England Nuclear, Wilmington, DE) was infused intravenously to determine NE kinetics.
Plasma samples were obtained to measure endogenous and [³H]NE concentrations, as we have previously described (33).
Briefly, samples were drawn into cooled tubes with EGTA and reduced glutathione (Amersham, Arlington Heights, IL),
placed on ice, and centrifuged at 4°C. Samples of the [³H]NE-infusion solution were collected, stored, and later assayed, as
described below for the plasma samples, to allow determination of the actual rate of [³H]NE infusion. NE and Epi concentrations were measured by using HPLC, using electro-
chemical detection with 3,4-deoxyepinephrine as the internal standard, a modification of our earlier method (17). The
HPLC effluent coinciding with the NE peak was collected and counted by liquid scintillation. This separation method al-
lowed determination of the plasma concentration of [³H]NE without interference from tritiated metabolites. Calculations for
the determination of NE kinetics by using the isotope dilution method were performed as follows: NE plasma clearance from the whole body (systemic clearance) = [³H]NE infusion rate/V*; the rate at which NE entered plasma for the whole body (systemic spillover) = systemic clearance × V, where V and V* are the concentrations of endogenous and [³H]NE, respectively.

Role of RAS. Six sheep served as their own controls in paired experiments consisting of PGI₂ infusion alone and
with the concomitant infusion of the angiotensin II (ANG II)-receptor antagonist L-158,809 (graciously provided by Merck,
Rahway, NJ). L-158,809 was initially reconstituted in 30 ml of sodium bicarbonate and then diluted further with 5% dext-
rose in water to give a final concentration of 0.3–0.5 mg/ml. This solution was filtered through a 0.45-µm Millipore filter
(Millipore, Bedford, MA) and was infused by using a 60-ml syringe in a Harvard pump (Harvard Apparatus, Dover, MA).
A loading dose of 0.3 mg/kg iv was given, followed by 0.3 mg·kg⁻¹·h⁻¹, both during the infusion of prostacyclin and for
60 min after the infusion ceased. This dose of L-158,809 was chosen after performance of dose-response curves with ANG
II in the presence and absence of the inhibitor. The dose employed produced a greater than log shift in the dose of ANG
II required to increase arterial blood pressure >20% above baseline (data not shown). Baseline measurements were
obtained both before and 5 min after the administration of the loading dose of L-158,809. The coinfusion of PGI₂ and
L-158,809 consistently resulted in greater decreases in MAP at lower doses, compared with the control study, thus prohib-
iting titration up to 500 ng·kg⁻¹·min⁻¹ in four animals because of excessive hypotension. To control for the effect that
different doses of prostacyclin might have on the postinfusion rise of MAP, PGI₂ infusion was started in two sheep at 100
ng·kg⁻¹·min⁻¹, as in the other four studies, and titrated to a maximal dose of only 300 ng·kg⁻¹·min⁻¹ in both experi-
ments. Hemodynamic measurements were made at baseline, at 15-min intervals during infusion, and at 2, 5, 10, 15, 30,
and 60 min after abrupt discontinuation of the drug.

Measurement of plasma renin activity (PRA). In five sheep,
PRA was measured in plasma obtained from the arterial catheter at baseline, at peak infusion, and at 10 and 120 min
after cessation of PG12 infusion. The samples were placed on ice and centrifuged at 3,000 rpm for 10 min at 4°C. The supernatant plasma was stored at −70°C until assayed according to the method of Workman et al. (37). Briefly, the pH of each plasma sample was adjusted to 5.5, and 2,3-dimercapto-1-propanol and 8-hydroxyquinoline were added. Samples were incubated at 37°C, and 0.1 M Tris buffer was added. Aliquots (50 μl) of plasma at dilutions of 1:2, 1:10, and 1:50 were used in an angiotensin I (ANG I) competitive radioimmunoassay with a 20-h incubation at 4°C. Bound ligand was separated with dextran-coated charcoal in 0.01 M Tris and 0.135 M sodium chloride and the centrifuged at 5,000 g for 15 min. The supernatant was decanted and then charcoal pellet counted in a gamma scintillation counter.

Statistical analysis. The data are presented as means ± SE. Using Fisher’s least significant difference approach to multiple comparisons, we calculated the area under the curve for all six studies and after cessation of PG12 infusion, for both the control studies and those with the addition of L-158,809 or phenolamine. Utilizing the PC! Info software package (Retriever Data System, Seattle, WA), we then used the Wilcoxon signed rank test to compare the area under the curve for all six animals. Only if a significant difference was shown between the two curves were individual time points then compared, again using the Wilcoxon signed rank test. The Wilcoxon signed rank test was also used to determine statistically significant changes in PRA over time. Significance is reported at a level of P < 0.05.

RESULTS

Hemodynamic changes during infusion of PG12. Hemodynamic responses to PG12, in the presence and absence of L-158,809, are expressed as mean numerical data in Table 1 and as percent change from baseline in Fig. 1. The latter allows for correction of baseline physiological variability among animals. As noted in our previous studies (10), infusion of prostacyclin in normotensive, chronically instrumented, awake sheep results in tachycardia with a 67% increase in heart rate (from 88 ± 2 to 147 ± 10 beats/min) and a fall in MAP. The nadir in MAP (77 ± 6 mmHg; 86% of baseline) in these animals occurred well before cessation of PG12 infusion. After 30 min, most animals began to exhibit tachyphylaxis to the effects of PG12 despite increasing infusion rates. There was a gradual rise from the nadir value to a MAP of 82 ± 5 mmHg at the time PG12 infusion ceased. CO rose 33%, from 5.1 ± 0.3 to 6.8 ± 0.3 l/min, at the highest dose of PG12. There was no significant change in PAP, but, because of the rise in CO, PVR fell by >20% (from 1.8 ± 0.1 to 1.4 ± 0.4 Wood units) at the time of peak infusion.

Hemodynamic changes associated with phenolamine administration. In paired experiments with and without the addition of phenolamine, there was no difference in MAP, CO, or PAP between the two studies, either during infusion of PG12 or after termination of the infusion (Fig. 1). The maximal rise in MAP during the postinfusion period was 28.5 ± 7.5% in the control study and 33.5 ± 6.7% with phenolamine added. These values are significantly different from baseline. No change in hemodynamics occurred with the administration of phenolamine.

Measurements of NE and NE spillover. NE plasma levels (n = 4) reveal no significant change from baseline during the infusion of PG12 or for 2 h after stopping the infusion (Fig. 3). In addition, we determined NE spillover in two sheep, because an increase in NE clearance might mask changes occurring in NE release at the nerve terminal if only uncorrected NE plasma concentrations were measured. These measurements showed an increase in NE spillover at peak infusion, rising from 303 to 879 ng/min. After PG12 infusion ceased, at the time of hemodynamic overshoot, levels of NE spillover had returned to baseline.

Role of RAS. Blockade of the ANG II receptor with L-158,809 significantly altered the observed dose-response relationship to PG12 for hemodynamic variables (Table 1, Fig. 1). ANG II receptor blockade before initiation of PG12 infusion caused a slight elevation (7 ± 4 beats/min) in heart rate and a modest decrease (6 ± 2 mmHg) in MAP. There were no significant changes in pulmonary hemodynamics or CO. However, during the infusion of PG12, in the presence of the ANG II receptor antagonist, MAP fell progressively by >25% (from 97 ±

Table 1. Hemodynamic effects of PG12 infusion

<table>
<thead>
<tr>
<th>Time</th>
<th>L-158,809</th>
<th>BL-1</th>
<th>BL-2</th>
<th>Peak</th>
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<tr>
<td></td>
<td>2 min</td>
<td>5 min</td>
<td>10 min</td>
<td>15 min</td>
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<tr>
<td>HR, beats/min</td>
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<tr>
<td>−</td>
<td>88 ± 4</td>
<td>88 ± 2</td>
<td>147 ± 10</td>
<td>93 ± 5</td>
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<tr>
<td>+</td>
<td>95 ± 5</td>
<td>95 ± 5</td>
<td>137 ± 9</td>
<td>104 ± 7</td>
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<td>MAP, mmHg</td>
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<td></td>
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<tr>
<td>−</td>
<td>90 ± 5</td>
<td>90 ± 5</td>
<td>82 ± 5</td>
<td>105 ± 4</td>
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<tr>
<td>+</td>
<td>91 ± 4</td>
<td>91 ± 4</td>
<td>70 ± 4</td>
<td>87 ± 5</td>
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<td>PAP, mmHg</td>
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<tr>
<td>−</td>
<td>18 ± 1.4</td>
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<td>17.5 ± 1.3</td>
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<tr>
<td>+</td>
<td>85 ± 0.4</td>
<td>85 ± 0.4</td>
<td>75 ± 0.8</td>
<td>86 ± 1.0</td>
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<tr>
<td>PCWP, mmHg</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>−</td>
<td>75 ± 0.1</td>
<td>75 ± 0.1</td>
<td>85 ± 1.0</td>
<td>97 ± 0.7</td>
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<tr>
<td>+</td>
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<td>51 ± 0.4</td>
<td>64 ± 0.4</td>
<td>49 ± 0.4</td>
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<tr>
<td>CO, l/min</td>
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<tr>
<td>−</td>
<td>4.9 ± 0.3</td>
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<td>4.9 ± 0.3</td>
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<tr>
<td>+</td>
<td>1.8 ± 0.1</td>
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<td>PVR, Wood units</td>
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<tr>
<td>−</td>
<td>2.1 ± 0.1</td>
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<td>+</td>
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</table>

Values are means ± SE. PG12, prostaglandin I2; HR, heart rate; MAP, mean arterial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; PVR, pulmonary vascular resistance; L-158,809, angiotensin II receptor antagonist; BL-1, initial baseline before loading dose of L-158,809; BL-2, baseline 5 min after giving loading dose of L-158,809 and initial baseline in control study; Peak, peak infusion of PG12; Off (2, 5, 10, 15, 30, and 60 min), time after termination of PG12 infusion.
5 to 70 ± 5 mmHg) and did not tend to normalize before PGI₂ infusion ceased. This lack of tachyphylaxis was significantly different from the control study. The elevation in CO and decrease in PVR in the animals pretreated with L-158,809 were similar to those observed in the control study.

After prostacyclin infusion ceased, heart rate rapidly returned to baseline in both studies (Table 1) and was unaffected by ANG II receptor blockade. In the control experiment, in which the sheep did not receive L-158,809 (Fig. 1), MAP increased significantly above baseline within minutes of stopping the infusion of PGI₂ and reached a maximal level of 111 ± 5 mmHg (23% above baseline) 15 min into the period after infusion ceased. MAP remained elevated for >1 h after the infusion had been terminated. Pulmonary hemodynamics revealed an interesting pattern. In the immediate postinfusion period, there was a small but significant decrease in PAP (from 18.9 ± 1.2 to 17.8 ± 1.2 mmHg) and a subsequent rise to 22.1 ± 1.3 mmHg (20% above baseline) at 30 min. This initial decrease in PAP occurred in all sheep. CO decreased dramatically by >30% from peak values to 4.9 ± 0.4 l/min (P ≤ 0.05)
soon after the infusion of PGI$_2$ was stopped and remained slightly below baseline. Although PVR initially fell in the postcessation period, a late rise was observed, beginning at 30 min, indicating active vasoconstriction in the face of unchanging CO. By 60 min after cessation of prostacyclin, PVR increased by 17% above baseline, from 1.8 ± 0.1 to 2.1 ± 0.1 Wood units.

The addition of L-158,809 entirely prevented the postinfusion systemic pressor response. MAP remained below baseline throughout this period, and at all times MAP was significantly decreased compared with control studies (P < 0.05; Fig. 1). Changes in PAP were generally similar to those seen without ANG II receptor blockade, although the early decrease in PAP seen in the control group was not observed. CO fell by 23% from peak values to 4.9 ± 0.4 l/min after prostacyclin was stopped and did not change thereafter.

ANG II blockade prevented any increase in PVR above baseline during the postinfusion period. However, there was a slow return toward baseline and an increase of 53% (1.3 ± 0.1 to 2.0 ± 0.2 Wood units) by 30 min, which largely reflects the decrease in CO rather than an increase in transpulmonary pressure gradient. By 60 min after infusion ceased, a significant difference in PVR had developed between the two groups.

PRA. PRA was serially measured during and after cessation of prostacyclin infusion. As shown in Fig. 4, there was a >10-fold increase in PRA after infusion of PGI$_2$, from a baseline of 0.42 ± 0.06 to 4.5 ± 1.0 ng·kg$^{-1}$·h$^{-1}$ (P = 0.05) just before cessation. At 2 h after cessation of PGI$_2$, PRA remained elevated to a level more than three times the baseline level.

**DISCUSSION**

Numerous studies evaluating the effects of prostacyclin infusion in humans have noted worsening symptoms when the drug is transiently interrupted (2, 3, 21). Given the short half-life of PGI$_2$, it is likely that patients may experience hemodynamic deterioration during this time. Our prior investigations have shown that abrupt cessation of PGI$_2$ infusion in healthy sheep leads to systemic hypertension and decreased CO (10).

The present study documents a significant rise in PRA during infusion of prostacyclin that is sustained for up to 2 h after the infusion is stopped. These results are consistent with the known stimulatory effects of PGI$_2$ on release of renin as well as the 20–30 min half-life of renin. Because PRA is the rate-limiting enzyme in the formation of circulating ANG II, the increase that we have observed in PRA implicates ANG II as the culprit responsible for the pressor response that occurs after cessation of prostacyclin. Our ability to prevent the hypertensive response with an ANG II receptor antagonist provides further evidence for ANG II as the mediator of this phenomenon.

Although the shape of the two curves after infusion of prostacyclin are similar, we do not believe that the lack of MAP overshoot after cessation of infusion in the presence of ANG II blockade can be explained by a greater reduction in MAP. One would expect that a greater decrease in MAP would lead to greater release of renin and therefore a more robust vasoconstrictor rebound. Because the animals were no longer receiving a vasodilator, it is not surprising that MAP returned to baseline after PGI$_2$ infusion ceased.

Hypotension not only increases PRA but also stimulates catecholamine release. Therefore, it was reasonable to suspect that sympathoadrenal activation during PGI$_2$ infusion could lead to postcessation hypertension or at least contribute to it. We have done a type II test with the assumption that NE levels would have to increase by 100% or more to account for the postinfusion hypertensive overshoot. This assumption does not appear unreasonable, given the fact that PRA increased 10-fold over baseline values at peak infusion and remained more than seven times the baseline value by 10 min after the infusion had been terminated. We cannot exclude the possibility that sympathetic activation contributes to the postinfusion response; however, our calculations indicate that this is unlikely. Our present studies had a 73% power to detect such a difference.

Although circulating NE levels do not necessarily represent concentrations at target organs, they likely reflect the concentrations to which the endothelial surface and vascular smooth muscle are exposed. However, plasma NE concentration is dependent on both NE release into and NE clearance from the circulation. An increase in NE clearance can mask a change in NE spillover if only plasma NE levels are measured. Measurement of NE spillover corrects for changes in NE clearance that occur with fluctuations in CO and vascular surface area, thus providing a more accurate reflection of NE release into the circulation. Because levels of both plasma NE and NE spillover decreased after PGI$_2$ infusion ceased, this parallel change argues persuasively against a role for NE as a mediator of the postinfusion pressor response. The fact that catecholamines bind to $\beta_2$-receptors in the kidney, further stimulating renin release, could indeed augment the effect of PGI$_2$ and increase ANG II levels to an even greater extent in the postcessation period.

The hemodynamic changes observed in the systemic circulation were less marked in the pulmonary circula-

![Image](https://via.placeholder.com/150)

**Fig. 4.** Plasma renin activity measured at BL, peak infusion of PGI$_2$ (time 0), and at selected time points after termination of infusion. Solid bar, duration of PGI$_2$ infusion. Data points represent means ± SE; n = 5 sheep.
tion. This was not unexpected, because the pulmonary arteries of normal sheep are highly compliant vessels capable of accommodating large fluctuations in flow without significant alterations in pressure. The rise in PAP occurred later in the postcessation period and was sustained at 60 min; however, the maximal pressure change was only 4 mmHg. PVR during this time, analyzed as a percent change from baseline, revealed increasing resistance with PGI₂ infusion alone compared with decreasing resistance when L-158,809 was coadministered. In large part, this reflects the persistent decrease in CO below baseline in the control study, which was prevented with the addition of an ANG II receptor antagonist.

We are uncertain as to why this mild rebound in PAP was delayed after cessation of PGI₂, but it was not prevented by ANG II receptor blockade, suggesting a different mechanism from the one that governs postinfusion hemodynamic changes in the systemic circulation. We have assumed that during the infusion of prostacyclin the pulmonary vessels are fully vasodilated and recruited. This may not be the case, because of the high compliance of the pulmonary circulation, and a partially dilated or incompletely recruited vascular bed might hide early vasoconstriction that would otherwise be more prominent.

The results presented in this paper provide an explanation for the systemic hypertensive response after sudden interruption of prostacyclin infusion in sheep with a normal pulmonary circulation. A number of studies support the contention that, in a remodeled pulmonary vascular bed, hemodynamic changes would be more akin to those seen in the systemic circulation during, as well as after, PGI₂ infusion. Perkett et al. (29) showed increased pulmonary vasoreactivity in sheep that developed pulmonary hypertension after chronic air embolism. Christman et al. (9) and Badesch et al. (1) observed a decrease in endogenous PGI₂ metabolites in clinical and experimental pulmonary hypertension, respectively. Such perturbation in the autoregulatory function of the endothelium might tend to augment vasoconstriction. Cardinal features of PPH include medial hypertrophy and increased muscularization of the pulmonary arterial vasculature. Therefore, one might expect physiological changes similar to those seen in the systemic circulation in such patients.

There are reports indicating increased vasoreactivity associated with acute cessation of prostacyclin infusion in humans with PPH. Barst et al. (4) administered a bolus injection of PGI₂ during evaluation and treatment of a young girl with pulmonary hypertension; decreases in both systemic and PAP resulted. However, rebound hypertension developed in both circulations within minutes, and pressures remained elevated for nearly 1 h, despite start of a continuous infusion of PGI₂. It should be noted that the bolus dose administered was 10-20-fold greater than that usually given when continuous PGI₂ therapy was started in patients with PPH and was more analogous to the dose these patients receive during chronic infusion. Similarly, in studies of patients experiencing recurrent symptoms after transient interruption of PGI₂ infusion, Rubin and colleagues (31) did not observe improvement for 15-30 min after PGI₂ had been restarted. These findings lend support to the occurrence of a postcessation pressor response in humans as well as in animals. Indeed, in subjects without pulmonary hypertension, elevated ANG II levels have been measured during and after short infusions of PGI₂ (13, 25).

Although it is not unreasonable to assume that the mechanism we have shown to be responsible for systemic hypertension after abrupt cessation of PGI₂ infusion in sheep would also provide an explanation for the symptoms experienced by patients with PPH whose infusion is interrupted, our studies have certain limitations. It is conceivable that a different spectrum of mediators, such as TxA₂ or endothelin-1, could play a more significant role in humans, although the basic actions of ANG II and PGI₂ have been reported not to differ between species (12). Another criticism that can be directed at these studies is that they have evaluated only short-term effects of PGI₂ administration (~40 half-lives). However, based on the observations of Barst and associates (4), it appears that short-term administration of high doses of prostacyclin may adequately reflect the hemodynamic effects of long-term infusion. The use of such high doses of PGI₂ in our studies, although 50-fold greater than the usual starting dose in patients with PPH, is on the same order of magnitude as in patients receiving long-term infusion, some of whom are receiving a dose of >200 ng·kg⁻¹·min⁻¹. Finally, we did not evaluate the response to prostacyclin infusion in the presence of diffuse pulmonary arteriole. However, given the evidence presented by others for increased vasoreactivity, we might expect enhanced changes in a pulmonary circulation with hypertrophied vasculature and decreased cross-sectional area. Alternatively, minimal change in pulmonary arterial vasoreactivity, but a similar systemic pressor response in the presence of a compromised right ventricle (because of elevated PAP), might produce significant hemodynamic instability.

In conclusion, we have shown that activation of the RAS appears to be responsible for systemic hypertension occurring after the abrupt cessation of PGI₂ infusion in sheep. Blockade of ANG II receptors abolishes this response. Sympathoadrenal activation resulting from vasodilation does not appear to play a significant role in this phenomenon. Although we have not shown that postinfusion hypertensive changes occur in an altered pulmonary vascular bed, it is likely that rebound hypertension (pulmonary and/or systemic) occurs after interruption of chronic PGI₂ infusion in patients with PPH. Further experiments are underway in patients with PPH, to evaluate the response to prostacyclin after infusion ceases. Finally, we speculate that ANG II receptor antagonists may be clinically useful in a substantial number of patients receiving short-acting parenteral vasodilators.

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