Inhaled prostacyclin is safe, effective, and affordable in patients with pulmonary hypertension, right heart dysfunction, and refractory hypoxemia after cardiothoracic surgery

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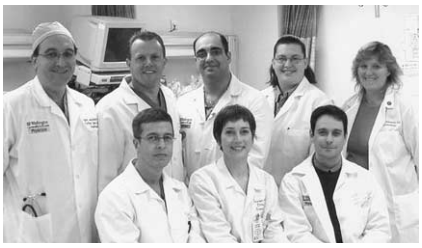

Jacobsohn, Affleck, Moazami, Smith, and Tymkew (standing, left to right). De Wet, Hill, and Avidan (sitting, left to right).

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Background: The purpose of this study was to describe our institutional experience in using inhaled prostacyclin as a selective pulmonary vasodilator in patients with pulmonary hypertension, refractory hypoxemia, and right heart dysfunction after cardiothoracic surgery.

Methods: Between February 2001 and March 2003, cardiothoracic surgical patients with pulmonary hypertension (mean pulmonary artery pressure >30 mm Hg or systolic pulmonary artery pressure >40 mm Hg), hypoxemia (Pa_{O_2}/fraction of inspired oxygen <150 mm Hg), or right heart dysfunction (central venous pressure >16 mm Hg and cardiac index <2.2 L · min^{-1} · m^{-2}) were prospectively administered inhaled prostacyclin at an initial concentration of 20,000 ng/mL and then weaned per protocol. Hemodynamic variables were measured before the initiation of inhaled prostacyclin, 30 to 60 minutes after initiation, and again 4 to 6 hours later.

Results: One hundred twenty-six patients were enrolled during the study period. At both time points, inhaled prostacyclin significantly decreased the mean pulmonary artery pressure without altering the mean arterial pressure. The average length of time on inhaled prostacyclin was 45.6 hours. There were no adverse events attributable to inhaled prostacyclin. The average cost for inhaled prostacyclin was $150 per day. Compared with nitric oxide, which costs $3000 per day, the potential cost savings over this period were $681,686.

Conclusions: Inhaled prostacyclin seems to be a safe and effective pulmonary vasodilator for cardiothoracic surgical patients with pulmonary hypertension, refractory hypoxemia, or right heart dysfunction. Overall, inhaled prostacyclin significantly decreases mean pulmonary artery pressures without altering the mean arterial pressure. Compared with nitric oxide, there is no special equipment required for administration or toxicity monitoring, and the cost savings are substantial.

Because of a potential conflict of interest related to this manuscript on the part of our editors, Dr David A. Fullerton served as guest section editor, assigned reviewers, and made editorial decisions or recommendations leading to its acceptance for publication.

Pulmonary hypertension, right ventricular dysfunction, and perioperative hypoxemia are common problems that necessitate treatment in a cardiothoracic intensive care unit. Inhaled nitric oxide (iNO) was the first agent shown to be a selective pulmonary artery vasodilator, and it has also been shown to improve oxygenation in patients with acute lung injury and adult respiratory distress syndrome (ARDS).[1,2] Nitric oxide, however, has become prohibitively expensive and has several associated toxicities that necessitate monitoring, which further increases the cost.[3]

In the search for a selective pulmonary artery vasodilator, both as an alternative and possibly as a complement to iNO, several drugs administered via the inhalational route have been described in animal models and humans. These include inhaled sodium nitroprusside, nitroglycerin, class 5 phosphodiesterase inhibitors (such as zaprinast and sildenafil), milrinone, prostaglandin E_1 (PGE_1; alprostadil), PGI_2 (prostacyclin), and iloprost (the stable analog of PGI_2).[4] The use of intravenous PGI_2 was first described in 1978 in canine experiments.[5] As opposed to PGE_1, PGI_2 was shown not to have any pulmonary inactivation and was therefore 10 times more potent than a systemic vasodilator, even though its metabolite 6-keto-prostaglandin $F_1\alpha$ had few systemic vasodilator properties. However, intravenous PGI_2, as opposed to intravenous PGE_1, became an important pulmonary vasodilator in the treatment of pulmonary hypertension.[6] However, in some patients with pulmonary hypertension, the intravenous doses required to decrease pulmonary artery pressures (PAPs) are often so high that significant systemic hypotension occurs. In 1993, Welte and colleagues[7] reported that inhaled PGI_2 ($iPGI_2$) resulted in selective pulmonary artery vasodilation in dogs. It has been shown to be as effective as iNO in reducing pulmonary vascular resistance in heart transplant candidates,[8,9] in decreasing PAPs in primary and secondary pulmonary hypertension,[10] and in improving right ventricular function in animals with hypoxic pulmonary vasoconstriction[11]; it is also effective as a selective pulmonary artery vasodilator, with improvement in oxygenation in patients with ARDS.[12-14] Compared with iNO, it is less expensive, is easier to administer, is relatively free of side effects, and requires no special toxicity monitoring.

The manufacturer has not sought Food and Drug Administration (FDA) approval for inhalational administration of PGI_2. The objective of this case series was to report our institutional experience with $iPGI_2$ in critically ill cardiothoracic surgical patients. Our secondary aim was to determine whether it is easy to use during surgery as well as in the intensive care setting and to perform a cost analysis comparing it with iNO.

Methods

The Human Studies Committee at Washington University Medical School approved the study, and all enrolled patients signed written, informed consent. Before initiation of the study, the principal investigator (E.J.) obtained an investigational new drug application from the FDA. This was done so we could investigate a new route of administration of a previously approved drug.

One hundred twenty-six patients (67 men and 59 women with a mean age of 56 ± 15 years) were enrolled in this prospective, interventional study of $iPGI_2$. The inclusion criteria were cardiothoracic surgery patients with pulmonary hypertension, right ventricular dysfunction, or refractory hypoxemia in the perioperative period. Pulmonary hypertension was defined as a mean PAP (MPAP) 30 mm Hg or more or systolic PAP 40 mm Hg or more. Right ventricular failure was defined as a central venous pressure (CVP) 16 mm Hg or more and cardiac index less than 2.2 $L \cdot min^{-1} \cdot m^{-2}$. Refractory hypoxemia was defined as a ratio of arterial partial oxygen pressure to fraction of inspired oxygen (Pa_{O_2}/F_{IO_2} ratio) less than 150 mm Hg. Clinicians first attempted to improve oxygenation by conventional methods. These included strategies such as: 1) increasing the inspired oxygen tension, 2) optimizing functional residual capacity with the best positive end-expiratory pressure (PEEP) and recruitment maneuvers, 3) optimizing the inspiration-expiration ratio, 4) selecting the most appropriate mode of mechanical ventilation, and 5) using neuromuscular blockade when indicated. The exclusion criteria were patients younger than 18 years of age, pregnant patients, and those with a known allergy or sensitivity to PGI_2 or the diluent (glycine). Hemodynamic variables were measured before the initiation of $iPGI_2$, 30 to 60 minutes after the initiation, and every 6 hours thereafter. The study was designed to optimize patient safety and ease of use while maintaining clinician autonomy. Clinicians were free to titrate inotropes, vasoconstrictors, or vasodilators to maintain mean arterial blood pressure (MAP), cardiac output, or both. Side effects attributable to the use of $iPGI_2$ were recorded. All adverse events were reported to the Human Studies Committee and then reviewed by a data safety monitoring committee for a further in-depth review.

PGI_2 is supplied as a sodium salt of epoprostenol (Flolan; Glaxo Wellcome Inc, Research Triangle Park, NC). It is reconstituted in 50 mL of glycine buffer diluent (sterile diluent for Flolan) to a final concentration of 20,000 ng/mL. It is then nebulized by using a continuous nebulizer system (MiniHEART nebulizer; Westmed, Tucson, Ariz). This is attached to the inspiratory limb of the ventilator circuit or via face mask with a Venturi attachment for aerosolization. For continuous administration, a 60-mL syringe of PGI_2 (20,000 ng/mL) is attached to a standard intravenous pump and delivered at a constant rate of 8 mL/h to the nebulizer chamber. The nebulizer chamber is primed with 15 mL of the PGI_2 solution, and at a nebulizing oxygen flow rate of 2 to 3 L/min, approximately 8 mL/h is nebulized. The glycine buffer diluent is "sticky," and we therefore decided to empirically change filters on the ventilator every 2 hours to prevent ventilator valve malfunction. To support continuous nebulization, a heated wire circuit was added to the ventilator. The $iPGI_2$ concentration was weaned by 50% every 2 to 4 hours until a concentration of 2500 ng/mL was reached (20,000 to 10,000 to 5000 to 2500 ng/mL), as long as the patient did not have a negative response. A negative response was

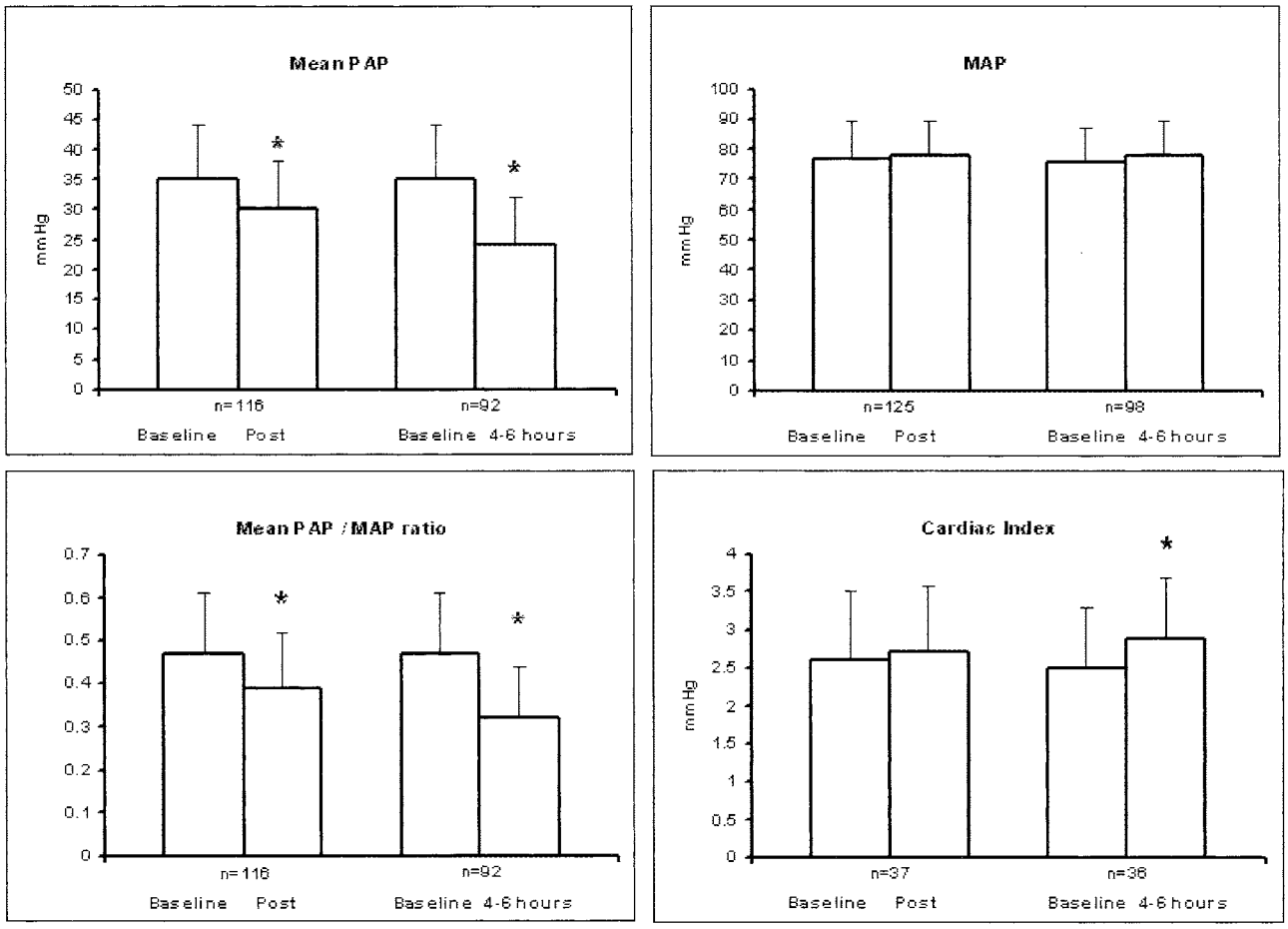

Figure 1. Effect of $iPGI_2$ on MPAP, MAP, the MPAP/MAP ratio, and cardiac index for all patients: $P < .001$. The smaller number of patients at the 4- to 6-hour time periods are compared with their own baseline. The numbers at this time period are smaller because some of the original patients were no longer receiving $iPGI_2$ or had incomplete data.

defined as an increase in PAP by 15% or a decline in cardiac index or the Pao_2/Fio_2 ratio by 10%. Systemic arterial pressure was closely monitored, and the PGI_2 dose was adjusted accordingly if a clinical change in blood pressure was observed.

The major aim of this study was to evaluate the immediate and sustained effects of $iPGI_2$ on PAPs in patients with pulmonary hypertension, right ventricular dysfunction, and refractory hypoxemia. Previous studies have shown reductions in MPAP of at least 8 mm Hg (SD, 7.5 mm Hg) with $iPGI_2$. On the basis of these findings, 9 patients would be required to demonstrate a mean decrease in PAP of 8 mm Hg (SD, 8 mm Hg) with a power of 90% and a P value of .05. With the large number of patients we were planning to recruit (>100), the study was adequately powered to detect effects of $iPGI_2$ on PAP in each subgroup.

The Shapiro-Wilke test of normality was used to assess the distribution of the continuous data. Variables were normally distributed. Paired Student t tests were used to evaluate the changes seen in hemodynamic and oxygenation parameters. The SPSS statistical package (SPSS, Chicago, Ill) was used for all analyses. A post hoc analysis of patients with refractory hypoxemia was performed.

Results

One hundred twenty-six patients were prospectively enrolled during the study period. The demographics are shown in Table 1. The average time on $iPGI_2$ was 45.6 hours (range, 0.1-390 hours). Tables 2 through 7 show the analysis for the 3 groups of patients that were enrolled. At both time points (after initiation and at 4-6 hours), $iPGI_2$ significantly decreased the MPAP. The ratio of MPAP to MAP improved significantly at both time points. Further, no significant changes were observed in MAP at the same time points, demonstrating the selective pulmonary effects of $iPGI_2$. The effect of $iPGI_2$ on all hemodynamic parameters is reported in Tables 8 and 9. Although the entire group did not show an improvement in the Pao_2/Fio_2 ratio, post hoc analysis

showed that in patients with refractory hypoxemia, there was a significant improvement in the Pao_2/Fio_2 ratio (Tables 2 and 3). The initial Pao_2/Fio_2 increased from 85 ± 33 to 158 ± 114 ($P = .001$). For those patients with refractory hypoxemia who remained on the treatment at 4 to 6 hours, the Pao_2/Fio_2 ratio increased from 95 ± 36 to 186 ± 111 ($P = .001$).

There was a substantial cost savings compared with iNO. The total cost for administering $iPGI_2$ is approximately $150 per day. The cost for iNO is $125 per hour, or $3000 per day. Total patient hours of $iPGI_2$ administration were 5740.50 hours. The total $iPGI_2$ cost was $35,878, versus a calculated nitric oxide cost of $717,564. This amounts to a calculated cost savings of $681,686.

There were few adverse events attributable to $iPGI_2$. No patients complained of facial flushing. There was no significant systemic hypotension. There were no clinically significant bleeding events. Within 30 days, there were 2 re-explorations for postoperative bleeding (2/126; 1.6%), 6 cases of renal failure (6/126; 1.6%), and 1 new stroke (1/126; 0.8%). There were 2 perioperative cardiac arrests (2/126; 1.6%). There was 1 serious adverse event related to the use of the "sticky" glycine diluent. An exhalation valve on a ventilator became stuck, and this resulted in significant auto-PEEP and hypotension. The problem was diagnosed early, and there were no sequelae. On several patients, the mainstream end-tidal CO_2 analyzers ceased to function because of excess moisture accumulation. The overall 30-day mortality rate was 12.7%.

TABLE 1. Demographics (n = 126)

Variable	Data
Age (y) (mean ± SD)	56 ± 15
Weight, (kg) (mean ± SD)	77 ± 22
Sex	
Male	67
Female	59
Cardiac operation	78
CABG	17
CABG + valve	11
Valve	17
Heart transplantation	12
LVAD	15
Other*	6
Lung transplantation	43
Thoracic operation	5
Enrollment criteria†	
Pulmonary hypertension	110
RV dysfunction	14
Refractory hypoxemia	32

CABG, Coronary artery bypass graft; *LVAD,* left ventricular assist device; *RV,* right ventricular.
*Other cardiac operations included atrial septal defect repair, maze-atrial septal defect, pulmonary thromboendarterectomy, post-extracorporeal membrane oxygenator removal after redo-aortic valve replacement, thoracoabdominal aortic aneurysm repair, post–chest wound re-exploration.
†Note that some patients met more than 1 of the 3 inclusion criteria.

Discussion

Inhaled aerosolized PGI_2 has been described in a number of small human studies for use in patients with ARDS,[12-15] primary and secondary pulmonary hypertension,[10,16] and right ventricular failure or dysfunction[9,17] and to improve oxygenation.[18,19] It has also been shown to be as effective as iNO.[8,12,13,20-22] However, centers that use $iPGI_2$ use it via a non–FDA-approved route of administration. Similarly, iNO used for indications other than pulmonary hypertension is used for a non–FDA-approved indication. After obtaining a FDA investigational new drug application, we set out to document and demonstrate its efficacy, safety, ease of administration, and cost in a large cardiothoracic surgical operating room and intensive care unit. We found that $iPGI_2$ was effective as a selective pulmonary artery vasodilator in patients with pulmonary hypertension and right ventricular dysfunction, and improved oxygenation in patients with refractory hypoxemia. It acutely decreased PAPs while MAP was maintained. This resulted in an improvement in the MPAP/MAP ratio. Inhaled PGI_2 was also effective in improving oxygenation regardless of the etiology of hypoxemia. In patients with poor oxygenation, $iPGI_2$ not only improved oxygenation, but was also effective as a pulmonary vasodilator while maintaining MAP and cardiac output. Our study also demonstrates that there did not seem to be any appreciable tolerance to any of the beneficial effects after 4 to 6 hours of administration.

Inhaled PGI_2 binds to subunits of the prostaglandin G/protein receptor, which results in an increase in cyclic adenosine monophosphate,[23] as opposed to iNO, which results in an increase in cyclic guanosine monophosphate.[3] Many of iNO's associated toxicities are thought to be related to the increase in cyclic guanosine monophosphate that interferes with normal cellular proliferation, including DNA strand breaks and potential mutagenic base alterations.[3] PGI_2 has a short half-life of 5 minutes. It is rapidly hydrolyzed at acid or physiologic pH to 6-keto-prostaglandin $F_1\alpha$,[24,25] which has been shown to have few vasodilator properties.[5] As opposed to PGE_1 (alprostadil), which is commonly used to prevent reperfusion injury or as an intravenous pulmonary artery vasodilator in the perioperative period, intravenous PGI_2 is not inactivated in the pulmonary circulation. Because of this lack of pulmonary inactivation, PGI_2 is 10 times more potent as a systemic vasodilator than PGE_1.[5]

As with iNO, there are theoretical concerns regarding the potential antiplatelet effects of PGI_2 and its metabolite 6-keto-prostaglandin $F_1\alpha$.[24,26] Platelet/endothelial cell adhesion is regulated by endothelial cell–derived mediators, including PGI_2 and endothelium-derived relaxing factor. PGI_2

TABLE 2. Hemodynamic parameters for patients with refractory hypoxemia: baseline and after $iPGI_2$

Variable	Before $iPGI_2$	After $iPGI_2$	n	*P* value
Pa_{O_2}/F_{IO_2} ratio	85 ± 33	158 ± 114	27	.001
MAP (mm Hg)	77 ± 11	75 ± 10	32	.331
PAP (mm Hg)	32 ± 9	28 ± 9	26	.014
MPAP/MAP ratio	0.43 ± 0.13	0.35 ± 0.20	26	.039
CI ($L \cdot min^{-1} \cdot m^{-2}$)	2.7 ± 1.1	2.6 ± 0.7	13	.504
CVP (mm Hg)	17 ± 6	17 ± 7	24	.358
Wedge (mm Hg)	21 ± 4	17 ± 2	2	.5
PVR ($dynes \cdot s \cdot cm^{-5}$)	191 ± 47	179 ± 146	2	.892
SVR ($dynes \cdot s \cdot cm^{-5}$)	1315 ± 655	1163 ± 364	8	.297

$iPGI_2$, Inhaled prostacyclin; *MAP,* mean arterial blood pressure; *PAP,* pulmonary artery pressure; *MPAP,* mean pulmonary artery pressure; *CI,* cardiac index; *CVP,* central venous pressure; *PVR,* pulmonary vascular resistance; *SVR,* systemic vascular resistance.

TABLE 3. Hemodynamic parameters for patients with refractory hypoxemia: baseline and after 4 to 6 h on $iPGI_2$

Variable	Before $iPGI_2$	4 to 6 h after	n	*P* value
Pa_{O_2}/F_{IO_2} ratio	95 ± 36	186 ± 111	17	.001
MAP (mm Hg)	76 ± 11	78 ± 12	25	.465
PAP (mm Hg)	32 ± 7	26 ± 9	22	<.001
MPAP/MAP ratio	0.44 ± 0.11	0.34 ± 0.15	22	.001
CI ($L \cdot {}^{-1} \cdot m^{-2}$)	2.4 ± 0.5	2.6 ± 0.6	10	.635
CVP (mm Hg)	18 ± 5	15 ± 6	22	.015
Wedge (mm Hg)	20 ± 4	16 ± 0	2	.41
PVR ($dynes \cdot s \cdot cm^{-5}$)	212 ± 78	139 ± 23	2	.307
SVR ($dynes \cdot s \cdot cm^{-5}$)	1147 ± 414	1069 ± 218	7	.708

$iPGI_2$, Inhaled prostacyclin; *MAP,* mean arterial blood pressure; *PAP,* pulmonary artery pressure; *MPAP,* mean pulmonary artery pressure; *CI,* cardiac index; *CVP,* central venous pressure; *PVR,* pulmonary vascular resistance; *SVR,* systemic vascular resistance.

TABLE 4. Hemodynamic parameters for patients with pulmonary hypertension: baseline and after the initiation of $iPGI_2$

Variable	Before PGI_2	After PGI_2	n	*P* value
Pa_{O_2}/F_{IO_2} ratio	300 ± 184	319 ± 168	55	.322
MAP (mm Hg)	76 ± 12	78 ± 11	109	.148
PAP (mm Hg)	36 ± 9	30 ± 8	107	<.001
PAP/MAP ratio	0.49 ± 0.14	0.40 ± 0.12	107	<.001
CI ($L \cdot min^{-1} \cdot m^{-2}$)	2.6 ± 0.9	2.8 ± 0.9	30	.054
CVP (mm Hg)	18 ± 7	18 ± 8	78	.22
Wedge (mm Hg)	18 ± 2	18 ± 3	11	.933
PVR ($dynes \cdot s \cdot cm^{-5}$)	358 ± 164	246 ± 122	11	.005
SVR ($dynes \cdot s \cdot cm^{-5}$)	1199 ± 483	1093 ± 390	19	.291

$iPGI_2$, Inhaled prostacyclin; *MAP,* mean arterial blood pressure; *PAP,* pulmonary artery pressure; *CI,* cardiac index; *CVP,* central venous pressure; *PVR,* pulmonary vascular resistance; *SVR,* systemic vascular resistance.

activates platelet adenylate cyclase and augments cyclic adenosine monophosphate formation by way of specific membrane receptors. van Heerden and colleagues[14] demonstrated that even though significant levels of 6-keto-prostaglandin $F_1\alpha$ could be demonstrated in patients receiving $iPGI_2$ for ARDS, there was no effect on platelet aggregation as measured by the response to adenosine diphosphate. In a double-blind, placebo-controlled randomized study over 4 to 6 hours of administration of $iPGI_2$, Haraldsson and associates[27] reported that even though antiplatelet effects could be detected by in vitro measurements such as platelet aggregation and thromboelastography, these effects were not clinically detected as measured by chest tube output and bleeding times after on-pump cardiac surgery. On the basis of these findings, we therefore did not monitor blood levels of either PGI_2 or its metabolite. Our results corroborate this because the re-exploration rate for bleeding was low. In contrast to the increasing bleeding times, there is also a theoretical concern that when platelets are exposed to extended periods of PGI_2 or its chemical analogs it may result in a time- and dose-dependent desensitization of the prostacyclin receptor.[28] Darius and associates[28] showed that

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