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REVIEW

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# Prostacyclin ($PGI_2$): new aspects of an old substance in the treatment of critically ill patients

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## Introduction

It is now 20 years since Moncada and Vane discovered prostaglandin $I_2$ ($PGI_2$) [1] and named it "prostacyclin". Since then, interest in the theoretical background and clinical application of this natural agent has increased continuously. This review summarizes the pharmacological properties and endogenous role of $PGI_2$. Furthermore, clinical applications (in particular of its analogue epoprostenol) are discussed, with special emphasis on the treatment of critically ill patients suffering from sepsis and/or pulmonary hypertension, either associated with the acute respiratory distress syndrome (ARDS) or of other origin (e.g., after cardiac surgery). In this context we also point out recent advances concerning the transbronchial delivery route as opposed to intravenous infusion and compare its effects to that of nitric oxide (NO) inhalation.

## Pharmacological properties

Like the other members of the prostaglandin family of lipid mediators, prostacyclin ($PGI_2$; chemically 9-deoxy-6,9α-epoxy-delta$^5$-$PHF_1\alpha$) is derived from endoperoxide intermediates of arachidonic acid through the microsomal pathway of fatty acid metabolism by the constitutive isoform (COX-1) of cyclooxygenase (Fig. 1). Sites of $PGI_2$ production include vascular tissues of all kinds, in particular endothelial cells, and smooth muscle cells up to the adventitia of arterial and, to a lesser extent, venous vessels. $PGI_2$ is also synthesized in interstitial kidney cells, gastric mucosal epithelial cells, leukocytes, and skin fibroblasts. The rate-limiting step in prostaglandin synthesis is mediated by phospholipase $A_2$, an enzyme known to be stimulated by bradykinin and several cytokines. Total endogenous $PGI_2$ production amounts to about $60\ pg \cdot kg^{-1} \cdot min^{-1}$, producing plasma levels between 5 and $18\ ng \cdot l^{-1}$ or $0.2–0.5\ nmol \cdot l^{-1}$.

$PGI_2$ is chemically unstable (depending on pH), as indicated by the rather short half-life of 2–3 min in the circulation at physiological pH. It hydrolyzes spontaneously to the stable 6-oxo-prostaglandin $F_1\alpha$, an ineffectual and non-toxic stable metabolite which is eventually eliminated by the kidneys (Fig. 1).

However, unlike other prostaglandins (in particular of the E series), $PGI_2$ is not inactivated in the pulmonary circulation [2] but produced and released into the systemic circulation by endothelial cells within the pulmonary vasculature, so that the difference between arterial and venous plasma levels is negligible [3].

$PGI_2$ acts through specific membrane (so-called IP) receptors, which are coupled to the adenylyl cyclase system, probably by a $G_s$-protein [4]. Activation of the intracellular enzyme adenylyl cyclase by $PGI_2$ increases cyclic adenosine monophosphate (cAMP) concentrations in the effector cells, which in turn activates protein kinase A to decrease free intracellular calcium concentrations [5]. Recently, $PGI_2$ has been shown to increase membrane-bound guanylyl cyclase activity in bovine endothelial cells, raising new questions about its definitive intracellular signaling mechanism [6].

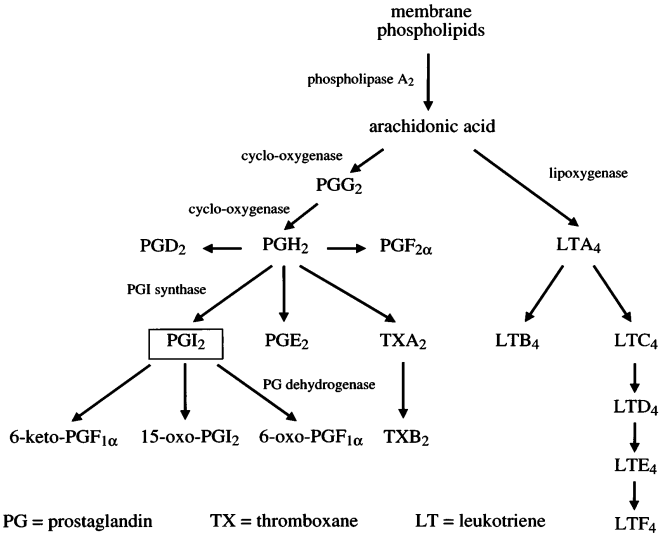


**Fig. 1** Biochemical pathway of eicosanoid synthesis and degradation

## Endogenous prostacyclin and its physiological relevance

$PGI_2$ is a paracrine mediator which strongly dilates all vascular beds studied [5]. Thus, $PGI_2$ relaxes vessels independent of size (from aorta to precapillary sphincters) and location (arterial and, to a lesser extent, venous, pulmonary, and systemic in any organ) in a dose-dependent manner. The vasodilator activity of $PGI_2$ is predominantly on resistance vessels and is probably mediated by inhibition of the spontaneous myogenic reactivity of precapillary sphincters [7] and by direct relaxation of the vascular smooth muscle via increases in cAMP. Additionally, $PGI_2$ inhibits endothelin-1 secretion through guanylyl cyclase activation in bovine endothelial cells [6]. Therefore, endogenous $PGI_2$ may play a critical role in the regulation of blood pressure.

$PGI_2$ is the most potent inhibitor of platelet aggregation yet discovered [5]. Thus, it not only prevents thrombus formation but even disperses existing aggregates. Furthermore, $PGI_2$ prevents adhesion of platelets to vascular endothelium. Similarly, production of $PGI_2$ by the endothelium as well as topical application of exogenous $PGI_2$ analogues inhibit the adhesion of leukocytes to the vessel wall (even when microcirculatory blood flow is not affected), a mechanism which may be altered during endothelial injury of whatever origin [8, 9]. Finally, $PGI_2$ may inhibit the activation of leukocytes and monocytes during inflammatory reactions and reduce the release of lysosomal enzymes.

Several lines of evidence suggest that endogenous $PGI_2$ has an essential role in sepsis and other shock states. Endogenous $PGI_2$ formation is greatly increased during hemorrhagic [10] and endotoxic/septic shock [11–15] and during hypoxia [16], in particular in the splanchnic circulation. Enhanced release of $PGI_2$ during sepsis is probably caused by endotoxin-induced release of interleukin (IL)1 and tumor necrosis factor (TNF). A possible cause of the increased production of $PGI_2$ is the cytokine-mediated induction of the cyclooxygenase isoenzyme 2 (COX-2) [17]. By inference, since nonsteroidal antiinflammatory drugs do not effectively discriminate between the inducible and constitutive isoforms, $PGI_2$ production can be inhibited by this group of drugs [18], as well as by glucocorticoids, which selectively inhibit COX-2 and phospholipase $A_2$ [15, 19]. On the other hand, oxygen-derived free radicals, produced during reperfusion after acute hemorrhage in rats, inhibit splanchnic $PGI_2$ synthesis, leading to a marked decrease in splanchnic blood flow [12]. This has been reversed by pentoxifylline [20], a potent stimulator of $PGI_2$ formation in human blood vessels [21].

Therefore, there is strong evidence that $PGI_2$, among other endogenous vasoactive agents (e.g., NO and thromboxane (TX) $A_2$), is involved in the physiological regulation of vascular tone and thus determines local blood flow and pressure. Furthermore, endogenous $PGI_2$ seems to contribute to the hemodynamic abnormalities observed in various pathological states such as sepsis.

## Cytoprotection: possible mechanisms

Several observations indicate that $PGI_2$ (both endogenous and infused) also exerts cytoprotective effects, although the mechanisms involved are poorly understood. Experimental findings from cats in endotoxemic shock have revealed that $PGI_2$ almost completely prevents the accumulation in the blood of a myocardial depressant factor as well as cathepsin D, a marker of hepatocellular integrity, suggesting a stabilization of lysosomal membranes [22–24]. $PGI_2$ can reduce infarct size and oxygen demand and prevent reperfusion arrhythmias and enzyme release after experimental myocardial ischemia, regardless of whether it is administered before or during ischemia [25–27], suggesting that the protective effects are mediated by a stabilization of cell membranes [23]. Similar protective effects have been reported in patients with acute myocardial infarction who received $PGI_2$ infusion within 6 h of the onset of symptoms: plasma creatine kinase and lactate dehydrogenase were significantly reduced and extension of the infarction prevented compared to patients receiving placebo [28].

The protective role of endogenous $PGI_2$ release during reperfusion injury has also been shown indirectly in isolated, ischemic rabbit Langendorff hearts treated with indomethacin, in which the marked $PGI_2$ release during reperfusion was completely inhibited [29]. This was associated with a substantial deterioration in myo-

cardial recovery despite only minor changes in coronary perfusion, suggesting an important role for endogenous $PGI_2$ in the preservation of myocardial function [29].

$PGI_2$ protects vital organs, including lung and liver, from endotoxic or bacterial injury and therefore might preserve organ function during sepsis. Thus, mice treated with C*orynebacterium parvum* and the NO synthase inhibitor L-NMMA showed the most severe hepatic injury histologically when endogenous $PGI_2$ synthesis was blocked by high dose aspirin compared to either treatment alone [30]. Further, the hepatic damage induced was reduced in a dose-dependent manner by the concurrent administration of exogenous $PGI_2$, as evidenced by reduced hepatocellular enzyme release [30]. In rats with experimentally induced acute necrotizing pancreatitis, exogenous $PGI_2$ significantly reduced histological damage, diminished secondary renal damage, decreased mortality, and prolonged survival time [31]. Additionally, $PGI_2$ prolonged organ function (liver) and reduced hypoxic damage [22] after warm ischemia in the splanchnic [32] and pulmonary circulation [33].

Possible mechanisms of these cytoprotective effects of $PGI_2$ include its ability to scavenge reactive oxygen species (ROS) produced during reperfusion [34] and to reduce the synthesis of mediators of the sepsis cascade such as TNFα by mononuclear leukocytes [35–37].

By inference, any selective increase in splanchnic blood flow (see below) induced by $PGI_2$ also mediates cytoprotective effects in this region, including the kidneys and the liver [38, 39]. For instance, this has been shown in dogs in which gastric mucosal damage induced by ethanol was effectively prevented by intravenous (i.v.) infusion of $PGI_2$ [39]. Further strong evidence of the cytoprotective effect in the splanchnic region derives from patients undergoing major abdominal operations, when large amounts of endogenous $PGI_2$ are released, in particular during eventration and traction of the small bowel. When this release is prevented by pretreatment with ibuprofen, elevated plasma endotoxin levels and bacterial translocation into mesenterial lymph nodes are detectable [40]. The critical role of $PGI_2$ in regulating splanchnic blood flow has been demonstrated before in rats: ROS produced during hemorrhage/reperfusion injury inhibited (endogenous) splanchnic $PGI_2$ synthesis, which contributed to a decrease in splanchnic blood flow [41].

### Effects on regional blood flow

Regional blood flow, in particular in the splanchnic circulation, has received attention recently, since reduced splanchnic perfusion and oxygenation may result in bacterial and endotoxic translocation through a disturbed mucosal barrier, which in turn promotes the development of sepsis and multiple organ failure [42]. Experimental studies have shown that $PGI_2$ selectively increases splanchnic blood flow in healthy, anesthetized animals [2, 38] as well as in animals with hemorrhagic [43] and endotoxic shock [24, 44], in those with acute necrotizing pancreatitis [31], and after warm ischemia in the splanchnic circulation [32], even when cardiac output and perfusion pressure were unaffected [32, 38].

In healthy volunteers, $PGI_2$ infusion increased mean hepatic blood flow by 41 % as measured by dye dilution [45]. As a consequence of this, infused $PGI_2$ increased the hepatic venous oxygen saturation from 54 to 67 % in five patients with impaired hepatic blood flow after major liver surgery but did not in patients with liver cirrhosis [46]. In another recent case report, the pathological values of arterio-hepatovenous oxygen content difference and gastric intramucosal pH (pHi) were reversed with $PGI_2$ in a patient with septic shock already resuscitated in global terms using volume and dobutamine infusions [47].

By using pHi obtained by tonometry as an indicator of splanchnic perfusion or oxygenation [48], it has been shown in several studies in severe sepsis that $PGI_2$ infusion is able to increase pathologically low pHi values in patients unresponsive to conventional therapy [49, 50]. Since a persistently low pHi is associated with an adverse outcome [48], the use of $PGI_2$ might contribute to decreased morbidity and mortality in such critically ill patients.

Regarding the site of action, $PGI_2$ seems to dilate vessels in the microcirculation preferentially, as evidenced by laser Doppler measurements of skin blood flow in patients with sepsis and after cardiac surgery [51, 52]. Extrapolating these observations to other vascular beds suggests increased oxygen and substrate delivery to tissues due to the enhanced microcirculatory blood flow.

## Therapeutic strategies

The major indications for $PGI_2$ therapy derive from its two main effects, vasodilation and inhibition of platelet aggregation. In contrast to the potentially broad range of therapeutic indications in which $PGI_2$ might be useful, current clinical practice is rather reserved, possibly because of a fear of provoking systemic hypotension.

Epoprostenol, a derivative of $PGI_2$, is available as a freeze-dried sodium salt (Flolan, Glaxo Wellcome) for administration to humans. Because of its short elimination half-life from the circulation (2 to 3 min), it has to be infused continuously and the clinical effects (including those on platelets) are limited to about 30 min, allowing precise titration of the dose-response. To obtain a stable solution for infusion, the salt is diluted in a glycine buffer, where the pH is maintained at between 10 and 11. The solution then has to be further diluted with saline and given through a separate infusion line to

**Table 1** Clinical doses of intravenous and inhaled $PGI_2$ for different indications

| Indication | Intravenous dose ($ng \cdot kg^{-1} \cdot min^{-1}$) | [Reference] | Inhaled dose ($ng \cdot kg^{-1} \cdot min^{-1}$) | [Reference] |
|---|---|---|---|---|
| Anticoagulation during hemodialysis | 0.25–4 | [94] | | |
| | 2–5 | [96] | | |
| | 4–5 | [89] | | |
| | 5 | [97] | | |
| | 7.7 ± 0.7 | [95] | | |
| Augmentation of tissue blood flow/oxygenation | 5 | [47, 56, 60] | 18 ± 9 | [50] |
| | 5–10 | [51, 52] | | |
| | 5–12.5 | [62] | | |
| | 10 | [49, 61] | | |
| Treatment of pulmonary hypertension | 2–6 | [71] | 2–20 | [79] |
| | 2–12 | [69] | 5 | [73, 74] |
| | 4 | [65, 66] | 6.6 ± 3–33.6 ± 12 | [70] |
| | 5–20 | [88, 102] | 7.5 ± 2.5 | [75] |
| | 8 | [68] | 17–50 | [67] |
| | 12.5–35 | [63, 64] | 18 ± 9 | [50] |
| | up to 30 | [103] | 51 | [82] |

avoid it being inactivated by acidic drugs (e.g., catecholamines).

Since $PGI_2$ does not undergo pulmonary inactivation, it can also be infused intravenously when systemic effects are clinically desirable. The doses for i.v. infusion range from 2 to 5 $ng \cdot kg^{-1} \cdot min^{-1}$ for anticoagulation during hemodialysis, from 5 to 15 $ng \cdot kg^{-1} \cdot min^{-1}$ to achieve most of the desired hemodynamic effects, and up to 35 $ng \cdot kg^{-1} \cdot min^{-1}$ in the treatment of severe pulmonary hypertension (Table 1). Interestingly, the doses of aerosolized $PGI_2$ used for inhalation vary considerably among patients but in general do not differ markedly from the i.v. ranges (Table 1), despite the likelihood of major loss of drug on its way to the site of action (i.e., the alveoli) because aerosol particles are retained in the delivery system, endotracheal tube, or airways. This suggests that the effective doses for inhaled $PGI_2$ are substantially lower than for i.v. administration.

## Sepsis

Since sepsis and septic shock are characterized by systemic vasodilation associated with low vascular resistance, high cardiac output, and low perfusion pressures despite adequate fluid therapy, a therapeutic strategy using a vasodilator agent like $PGI_2$ seems paradoxical. There are, however, several good reasons for using $PGI_2$ to correct regional abnormalities in perfusion, which are often present during septic states and lead to organ dysfunction or failure. Furthermore, since adequate oxygen transport to organs does not necessarily also guarantee oxygen delivery to any microvascular bed or tissue, $PGI_2$ might improve the impaired microcirculatory blood flow which may be present during sepsis, even in a state of global hyperperfusion. Finally, $PGI_2$ can reduce the microcirculatory vasodilation and prevent the cessation of spontaneous vasomotion induced by lipopolysaccharide (LPS) injection [9]. One possible explanation of this phenomenon lies in the consideration of sepsis as panendothelial damage associated with cellular dysfunction, leading to regional imbalance between vasoconstrictor ($TX A_2$) and vasodilator ($PGI_2$) metabolites of arachidonic acid metabolism, despite their greatly increased production [11, 14, 15]. In view of the size of the "organ" (endothelium, surface area approximately 3000 $m^2$ or 1–1.5 kg) and the physiological importance of $PGI_2$ stated above, the therapeutic use of exogenous $PGI_2$ seems justified.

Results from experimentation in animals with endotoxic shock show that $PGI_2$ exerts a variety of beneficial actions in different species. Thus, $PGI_2$ increases cardiac index [53] or oxygen delivery ($DO_2$) [44] and urine output [53] and decreases fibrin degradation products [53], microclot formation [54], and cathepsin D levels [22, 24, 53]. Furthermore, $PGI_2$ protects the lung against injury from endotoxin administration in sheep [55] and reduces the drop in platelet count after LPS infusion in rabbits [54]. It also diminishes the decrease in arteriolar blood flow and the extent of vasodilation, thus preventing the decrease in mean arterial blood pressure induced by LPS injection in anesthetized hamsters [9]. Additionally, $PGI_2$ reduces capillary leak and microvascular permeability in the same experimental setting (hamster cheek pouch) [9]. Finally, exogenous $PGI_2$ reduces the hepatic injury produced by injecting *Corynebacterium parvum* and L-NMMA in mice in a dose-dependent fashion [30]. These indicators of improved organ function were associated with a substantial rise in the survival rate of $PGI_2$-treated animals in some studies [9, 53, 54].

**Table 2** Clinical experience of the effects of $PGI_2$ on pulmonary and systemic hemodynamics and oxygenation in ARDS patients (*PAP* pulmonary artery pressure, *PCP* effective pulmonary capillary pressure, *RVEF* right ventricular ejection fraction, $PaO_2/FIO_2$ ratio of partial pressure of arterial oxygen to fractional inspired oxygen, *HR* heart rate, *CO/CI* cardiac output/index, $DO_2$ oxygen delivery, *SAP* systemic arterial pressure, ↑ increase, ↓ decrease, ↔ no change)

| Study | Number of patients | Delivery route | Dose ($ng \cdot kg^{-1} \cdot min^{-1}$) | Effects of $PGI_2$[a] on: Pulmonary hemodynamics | Pulmonary gas exchange | Systemic hemodynamics |
|---|---|---|---|---|---|---|
| Richardson et al. [102] | 1 | Intravenous | 5–20 | PAP ↓ | ↔ | Not described |
| Woodcock [103] | 1 | Intravenous | up to 30 | ↔ | ↔ | Not described |
| Bihari et al. [56] | 27 | Intravenous | 5 | PAP ↓ | $PaO_2$ ↓<br>Shunt ↑ | HR, CI, $DO_2$ ↑,<br>SAP ↓ |
| Radermacher et al. [63] | 9 | Intravenous | 12.5–35 | PAP ↓<br>PCP ↓ | ↔<br>Shunt ↑ | HR, CI, $DO_2$ ↑,<br>SAP ↓ |
| Radermacher et al. [64] | 8 | Intravenous | 12.5–35 | PAP ↓<br>RVEF ↑ | ↔<br>Shunt ↑ | HR, CI, $DO_2$ ↑,<br>SAP ↓ |
| Rossaint et al. [65] | 9 | Intravenous | 4 | PAP ↓ | $PaO_2/FIO_2$ ↓<br>Shunt ↑ | HR ↔, CI ↑,<br>SAP ↓ |
| Walmrath et al. [67] | 3 | Inhaled aerosol | 17–50 | PAP ↓ | $PaO_2/FIO_2$ ↑<br>Shunt ↓ | CO ↔,<br>SAP (↓) |
| | 1 | Intravenous | 10 | PAP ↓ | Shunt ↑ | CI ↑ |
| Pappert et al. [85] | 3 (children) | Inhaled aerosol | 2–20 | PAP ↓ | $PaO_2/FIO_2$ ↑<br>Shunt ↓ | CO + SAP ↔ |
| Rossaint et al. [66] | 10 | Intravenous | 4 | PAP ↓<br>RVEF ↑ | $PaO_2/FIO_2$ ↓<br>Shunt ↑ | HR ↔, CI ↑,<br>SAP ↓ |
| Bein et al. [74] | 8 | Inhaled aerosol | 5 | PAP ↓ | $PaO_2/FIO_2$ ↑ | HR, SAP ↔, CI (↓) |
| Walmrath et al. [75] | 16 | Inhaled aerosol | 7.5 ± 2.5 | PAP ↓ | $PaO_2/FIO_2$ ↑<br>Shunt ↓ | HR, CO, SAP ↔ |

[a] Note the dependency of the effects on the drug delivery route

The first clinical study of $PGI_2$ infusion in patients with acute respiratory failure associated with sepsis was performed almost 10 years ago [56]. Increased $DO_2$ was seen to be accompanied by an increase in calculated oxygen consumption (and hence extraction ratio) only in those patients who eventually died of irreversible multiple organ failure. It was concluded that $PGI_2$ unmasked covert tissue hypoxia in critically ill patients, possibly because $PGI_2$ recruited capillary beds that were shut down by mediators, blocked by activated white blood cells, or constricted as a consequence of vascular endothelial injury [57, 58].

$PGI_2$ has become a reasonable alternative to catecholamines in applying the so-called "oxygen flux test," because it has proved equally effective in increasing cardiac output or $DO_2$ [49, 59]. In this test, $DO_2$ is acutely increased (either by fluid administration, blood transfusion, or inotropic agents) and oxygen uptake ($VO_2$) monitored. If $VO_2$ increases, the therapeutic intervention is believed to be useful. Catecholamines, the most common agents used for this test, are known to stimulate cellular metabolism per se and thereby increase oxygen demand. However, this is not the case for a "pure" vasodilator like $PGI_2$. Hence, increases in $DO_2$ achieved using a drug without metabolic effects should allow the unmasking of any preexisting oxygen debt. This has been shown in severely ill patients with fulminant hepatic failure, who substantially increased their mean $VO_2$ by 29% after $PGI_2$ infusion, despite only moderate increases in cardiac output (+7%) and $DO_2$ (+6%) [60]. It was concluded that these patients had significant tissue hypoxia in association with a tissue oxygen debt, which was eventually reversed in part by $PGI_2$ infusion.

Numerous studies have shown an increase in $VO_2$ following an increase in $DO_2$, regardless of the method of measurement (Table 2). It has been suggested [51] that an increase in $VO_2$ in parallel with $DO_2$ seems to be a special feature of $PGI_2$, since it was not detectable using the α-adrenoceptor blocker phentolamine, despite a similar increase in $DO_2$. It was shown by laser Doppler flowmetry that the microcirculatory site of action might have been responsible for this difference in that only $PGI_2$ increased microvascular blood flow [51, 52].

Whether such increases in $VO_2$ reflect enhanced tissue aerobic substrate oxidation is debatable. Observations of the metabolization of stable glucose isotopes in septic patients have revealed that, in concert with $VO_2$, glucose oxidation was selectively increased by 14% with $PGI_2$, while endogenous glucose production and glucose turnover remained constant [62]. Thus, improv-

ing oxygen availability ($DO_2$) at the cellular level did indeed enhance $O_2$-dependent substrate metabolism during sepsis, as postulated previously [56]. On the other hand, these results suggest that increased $VO_2$ is secondary to energy (ATP) producing processes, and not only the cost of increased delivery.

In summary, $PGI_2$ administration in sepsis causes vasodilation (in particular in the capillary bed [51]) leading to improved tissue oxygen transport. Enhanced $DO_2$ may correct preexisting tissue hypoxia and enables the cells to consume more oxygen for energy production. The inhibition of platelet aggregation, formation of TX $A_2$, release of IL-1 and TNF, and activation and adhesion of leukocytes and macrophages may contribute to the salutary effects of $PGI_2$ in septic patients [57].

## $PGI_2$ in the treatment of pulmonary hypertension associated with ARDS

The acute respiratory distress syndrome in adults is a severe form of acute lung injury following direct (inhalational, e.g., aspiration, trauma, pneumonia) or indirect (hematogenous, e.g., bacterial sepsis or pancreatitis) insults. It is characterized by impaired gas exchange because of intrapulmonary shunt, and by pulmonary hypertension contributing to pulmonary edema and right ventricular dysfunction, as evidenced by decreased right ventricular ejection fraction (RVEF). These abnormalities contribute to the high mortality of 30–50 % associated with this syndrome. Therapeutic strategies have aimed at reducing pulmonary vascular resistance to lower right ventricular afterload. Furthermore, the accompanying decrease in pulmonary capillary pressure should diminish fluid filtration and thus reduce edema formation. Finally, cardiac index and, hence, $DO_2$ should be augmented, improving organ perfusion.

The effects of pulmonary vasodilation using $PGI_2$ have been evaluated in ARDS. Thus, i.v. infusion of $PGI_2$ significantly lowered mean pulmonary blood pressure (including capillary pressure), improved right ventricular function (i.e., increased RVEF), and increased cardiac output [63–66]. Unfortunately, $PGI_2$ (when given intravenously), like all vasodilators, augments intrapulmonary shunt flow and thus increases venous admixture to arterial blood [56, 59, 63–66] (Fig. 2A). This may be deleterious in patients with preexisting ventilation/perfusion inhomogeneities and impaired pulmonary gas exchange. The resultant decrease in arterial partial pressure of oxygen ($PaO_2$), however, is often compensated for by the increase in cardiac output, so that $DO_2$ may even increase [56, 59, 61–64, 66, 67] (Table 2). In acute respiratory failure presenting with severe hypoxemia and substantial preexisting shunt, $PGI_2$ may also

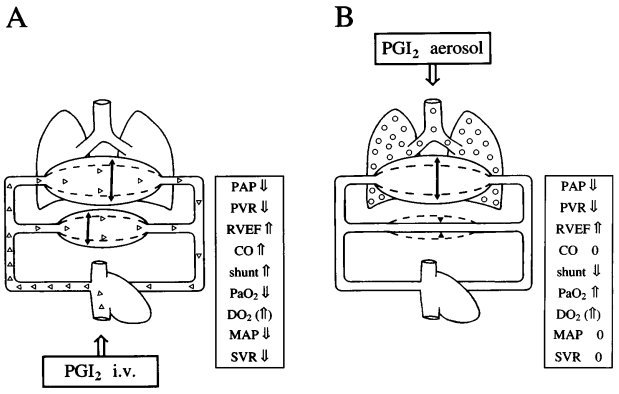


**Fig. 2** Schematic diagram of the pulmonary circulation in lungs from ARDS patients. Note the distribution of blood flowing through the lungs in relation to shunt flow. **A** During intravenous infusion of $PGI_2$, the amount of blood passing through poorly or nonventilated lung regions increases due to nonselective vasodilation of the pulmonary vasculature (i.e., also in regions with preexisting shunt flow). **B** Inhalation of aerosolized $PGI_2$, however, restricts the vasodilator effects to the ventilated areas of the lung, thereby reducing shunt flow. The hemodynamic and oxygenation effects of delivering $PGI_2$ by either route are summarized in the insets. Note the lack of systemic effects and the improvement of oxygenation during aerosolized $PGI_2$ inhalation **B** (*PVR* and *SVR* pulmonary and systemic vascular resistance, see Table 2 for other abbreviations)

improve pulmonary gas exchange without causing further deterioration in ventilation/perfusion mismatch [68]. However, $PGI_2$ (i.v. as well as inhaled) has no beneficial effects on gas exchange and oxygen transport in patients with coexisting parenchymal lung disease due to chronic obstructive pulmonary disease [69] or interstitial fibrosis [70].

To minimize the negative effects on gas exchange, it would be desirable to restrict pulmonary vasodilation to well-ventilated areas of the lung. In addition, systemic vasodilation should be avoided in ARDS to prevent further organ system failures as a consequence of reduced perfusion pressure. This has led to the concept of selective pulmonary vasodilation using the bronchial tree as a route of drug delivery. Subsequently, most studies have concentrated on gas inhalation, in particular of NO at concentrations between 5 and 80 parts per million (ppm) and have compared the effects with those obtained during i.v. vasodilator therapy. Inhalation of NO, as well as i.v. infusion of $PGI_2$, significantly reduced pulmonary artery pressure and increased RVEF in patients with ARDS [65, 66]. However, in contrast to inhaled NO, i.v. $PGI_2$ increased intrapulmonary shunt, thereby reducing arterial oxygenation [65, 66]. These and similar observations of the differences in systemic vasodilation (only i.v. $PGI_2$ decreased mean arterial blood pressure and resistance and increased cardiac output) support the view that selective pulmonary vasodilation with inhaled NO is superior to nonselective vasodilation in

both pulmonary and systemic vessels using i.v. $PGI_2$ [71]. Given the different routes of drug delivery, these results are not surprising, and the inhalation of aerosolized $PGI_2$ has recently been proposed. This should increase pulmonary and intrapulmonary selectivity by limiting the vasodilator effects to vessels in well-ventilated regions of the lung. Like inhaled NO, $PGI_2$ aerosol is transported by respiratory gas flow to ventilated alveoli, where it is absorbed and induces local vasodilation (Fig. 2B). However, because of the small amounts of drug reaching the alveolar space, spillover into the systemic circulation is negligible for most of the doses given clinically (see Table 1), thus confirming pulmonary selectivity and minimizing systemic side effects.

Experimental findings and several clinical reports suggest that this therapy could reduce increased venous admixture and consequently improve arterial oxygenation, while the effects on pulmonary arterial pressure were similar to those seen during systemic administration [67, 72, 73] (Table 2). In a recent study on eight patients with severe respiratory failure, nebulized $PGI_2$ ($5\ ng \cdot kg^{-1} \cdot min^{-1}$) decreased mean pulmonary blood pressure and improved gas exchange without any systemic effects [74]. Similar results, i.e., selective pulmonary vasodilation and improved oxygenation due to a reduction in shunt flow, have recently been reported in patients with severe pneumonia [70] and in those with ARDS [75].

In summary, increased pulmonary vascular resistance in ARDS can be lowered in a dose-dependent manner by i.v. $PGI_2$ infusion or inhalation of aerosolized $PGI_2$ to a maximum of 30–50 % in most patients. As a consequence, cardiac output and RVEF increase. Although i.v. infusion may be associated with an increase in pulmonary shunt with a resultant fall in $PaO_2$, $DO_2$ is often increased, as evidenced by a rise in mixed venous $O_2$ saturation. Systemic effects like decreased arterial pressure and vascular resistance can be prevented by using the inhalational route, which additionally may improve arterial oxygenation because of redistribution of blood flow from poorly or nonventilated (i.e., shunt) lung regions to those with a normal ventilation-perfusion ratio ("double selectivity"). In view of the fundamentally different efficacy profile of aerosolized $PGI_2$ compared to infused $PGI_2$ inhalation, has the potential to become a promising addition to the current clinical management of ARDS.

### *Inhaled $PGI_2$ by aerosol: comparison with nitric oxide*

Selective pulmonary vasodilation with inhaled NO has become widely accepted as a treatment option for pulmonary hypertension of whatever origin [76]. More recently, inhalation of aerosolized $PGI_2$ has been suggested as an alternative to NO. Unfortunately, there are several disadvantages associated with NO inhalation, including its potential cytotoxicity and high reactivity ($NO\cdot$ is a free radical) with membranes in the presence of $O_2$ leading to airway irritation, damage to lung tissue and depletion of surfactant, and high reactivity with hemoglobin causing methemoglobin and nitrosylhemoglobin formation with a subsequent decrease in $DO_2$. These potentially toxic effects of NO are related to its instability in the presence of molecular oxygen, resulting in conversion to higher oxides like nitrogen dioxide ($NO_2\cdot$), a gas 5–25 times as toxic as NO, or to peroxynitrite, a powerful oxidant. Furthermore, possible mutagenic effects of NO have been postulated. In addition, inhalation of NO for more than 24 h suppresses the neutrophil respiratory burst in children with pulmonary hypertension [77]. All of these possible side effects of NO inhalation require rigorous safety standards and continuous monitoring during use.

By contrast, $PGI_2$ and its stable degradation products do not have toxic side effects requiring special monitoring of respiratory or blood concentrations. Additionally, $PGI_2$ is easy to administer in the critical care setting as an aerosol using standard jet or ultrasound nebulizers connected to the inspiratory limb of the breathing circuit of conventional mechanical ventilators (Fig. 3) [67, 70, 73, 75, 78, 79].

Furthermore, because of its short biochemical halflife (about 2 min) and the transbronchial route of delivery, the extrapulmonary effects caused by spillover of $PGI_2$ into the systemic circulation are negligible. However, there are some practical aspects which should be addressed in this context. One uncertainty when using aerosol inhalation is how much drug is reaching the alveolar space, which is small ( < 5 % ) [80] and dependent on particle size and homogeneity, which in turn may vary with the type of nebulizer. Consequently, the dosages used are difficult to titrate and theoretically should be several times higher than those administered intravenously. In fact, the dosages used for aerosol inhalation producing similar or even superior effects ranged from 5 to $200\ ng \cdot kg^{-1} \cdot min^{-1}$, but were mostly only slightly higher than i.v. ones [50, 73–75, 81, 82] (Table 1). Therefore, the effective dose of inhaled $PGI_2$ at the site of action (i.e., perialveolar capillaries) is probably much lower, which might explain the lack of systemic effects. A second problem relates to longer term inhalation of aerosolized $PGI_2$. Since the aerosol is normally injected into the inspiratory limb of the ventilating circuit of nonrebreathing respirators with high inspiratory flow rates, large amounts of drug are usually required. Therefore, continuous delivery via infusion pumps (as shown in Fig. 3) is necessary to avoid frequent refilling, which may cause problems of "delivery lags" with short-term reversal, or even a rebound of the therapeutic effects. Finally, topical irritation of airway epithelial cells by $PGI_2$ and its alkaline buffer solution, in particular after

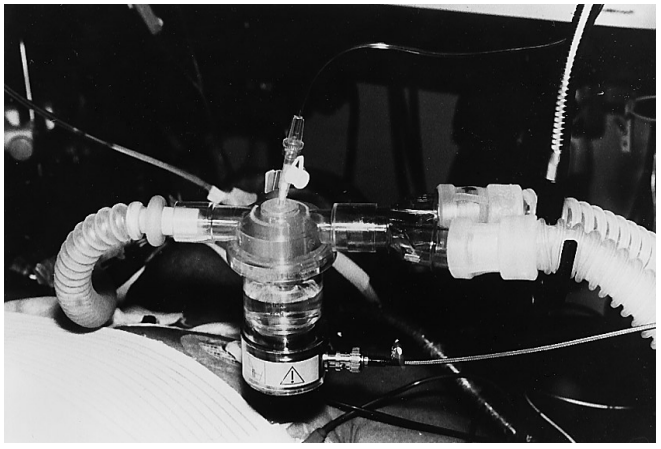

**Fig. 3** Aerosol delivery technique. $PGI_2$ buffer solution is delivered continuously to the chamber of the ultrasound nebulizer of the ventilator (Servo 300, Siemens) by an infusion pump. The dosage of $PGI_2$ aerosol delivered into the breathing circuit can be varied by the concentration of the added solution and by changing the ventilatory pattern (i.e. inspiratory flow, tidal and minute volume, ventilatory rate). Note the site of delivery close to the patient near the endotracheal tube

long-term application, cannot be ruled out completely, but this subject awaits further investigation. Recently, the inhalation of $PGI_2$ aerosol ($28\ ng \cdot kg^{-1} \cdot min^{-1}$) over a period of 8 h in healthy lambs did not produce acute pulmonary toxicity, as determined from the composition of the epithelial lining fluid obtained by bronchoalveolar lavage [83]. Thus, it appears that the bronchial system possesses a substantial capacity to buffer relevant amounts of aerosolized $PGI_2$ buffer solution used for clinical purposes (W. Seeger, Giessen, Germany, personal communication).

*Experimental findings.* Aerosolized $PGI_2$ reduced pulmonary artery pressure by 50% in dogs with hypoxic pulmonary vasoconstriction (without causing systemic vasodilation); however, this was less potent than the 75% reduction obtained using NO [72]. In a second study, the same group found a reduction in right ventricular afterload with only minor effects on cardiac output with both NO and aerosolized $PGI_2$, whereas RVEF was increased only with NO [81]. In anesthetized dogs with pulmonary vasoconstriction induced by a thromboxane analogue, however, both inhaled aerosolized $PGI_2$ and NO slightly reduced pulmonary arterial pressure, but failed to dilate substantially the pulmonary vessels, as evidenced by no shift of the pressure-flow relationship [84]. Additionally, oxygenation and intrapulmonary shunt, which were within the normal range in this study, were not affected by either drug [84]. The authors concluded that either the amount of aerosolized $PGI_2$ reaching the receptor sites within the lung were too small or, since NO was ineffective as well, thromboxane-induced pulmonary vasoconstriction in dogs is not an appropriate model for studying the effects of inhaled vasodilator agents. When comparing the effects of inhaled NO versus inhaled as well as i.v. $PGI_2$ in piglets with acute respiratory failure and pulmonary hypertension, improved oxygenation and pulmonary hemodynamics were identified without systemic vasodilation, suggesting pulmonary selectivity [85]. There was no significant difference between the two drugs when they were inhaled, but the effects were superior to i.v. infusions of $PGI_2$.

*Clinical experience.* This mainly derives from case reports of therapeutic attempts to control pulmonary hypertension unresponsive to conventional treatment. Only recently have studies with small numbers of patients been published [50, 75, 78, 82]. In general, the effects of inhaled $PGI_2$ aerosol on pulmonary hemodynamics do not seem to differ significantly from those of inhaled NO [50, 75, 78, 79, 82], and produce only marginal effects on systemic hemodynamics [50, 70, 75, 78, 79, 82]. Comparable effects on gas exchange have also been reported for both agents. In children with severe ARDS, oxygenation is improved to a similar extent with either aerosolized $PGI_2$ or inhaled NO, suggesting that $PGI_2$ also acts as a selective pulmonary vasodilator of well-ventilated lung regions [79, 82]. There are, however, differences in the time course of the effects on oxygenation: while the increase in $PaO_2$ is rapid in onset during NO inhalation, it takes almost 45 min to reach a similar increase with nebulized $PGI_2$ (Fig. 4). The same holds true for the decrease in $PaO_2$ after cessation of both drugs, as shown in a child suffering from ARDS (data from R. Rossaint, Berlin, Germany).

In adult patients suffering from ARDS and from pulmonary hypertension secondary to other pathologies, both inhaled NO and aerosolized $PGI_2$ effected selective pulmonary (but not systemic) vasodilation and redistributed blood flow from areas of shunt to well-ventilated regions with nearly identical efficacy profiles [75, 78]. The data from these well-conducted studies suggest that in patients with ARDS aerosolized $PGI_2$ may be a better pulmonary vasodilator than NO [78], whereas oxygenation is better improved by low-dose NO (mean dose 18 ppm) [75]. A possible explanation is the longer half-life of $PGI_2$ compared to NO, so that $PGI_2$ also reaches poorly or nonventilated lung regions, where it inhibits hypoxic vasoconstriction and thus increases intrapulmonary shunt. On the other hand, comparable effects on $PaO_2$ have been found with NO and $PGI_2$ in patients with pulmonary hypertension and septic shock, although only a minority of such patients responded to either therapy. Remarkably, aerosolized $PGI_2$, like i.v. $PGI_2$, but unlike inhaled NO, improved splanchnic perfusion, as suggested by an increase in pHi in these severely ill patients [50]. This phenomenon may also be

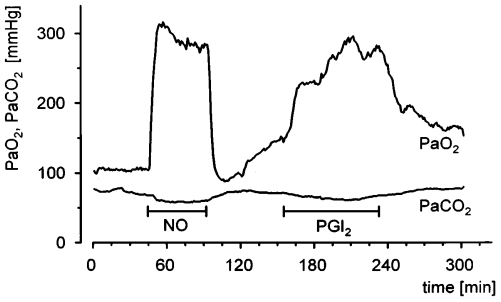


**Fig. 4** Effect of inhaled nitric oxide *NO* and aerosolized $PGI_2$ on blood gas tensions continuously monitored intraarterially in a child with ARDS. Note the different time course of oxygenation. (By courtesy of R. Rossaint, Klinik für Anästhesie und Operative Intensivmedizin, Universitätsklinikum Rudolf Virchow, Humboldt-Universität Berlin, Germany)

explained by the longer half-life of $PGI_2$ causing regional systemic effects, also in the absence of global systemic changes. Although not yet reported following inhalation of aerosolized $PGI_2$, serious rebound effects after sudden drug withdrawal should be anticipated, especially after longer term application.

The limited information available at present suggests that both inhaled NO and aerosolized $PGI_2$ produce equally effective selective pulmonary vasodilation in patients with pulmonary hypertension associated with ARDS. Second, both inhaled agents redistribute pulmonary blood flow from areas of shunt to well-ventilated regions and improve oxygenation to a similar extent.

## $PGI_2$ in the treatment of pulmonary hypertension after cardiac surgery

Severe pulmonary hypertension may be a life-threatening complication of cardiac surgery, particularly in children after corrective surgery for congenital heart disease. Although the exact mechanisms remain obscure, vasospasm of the pulmonary vasculature may be responsible, probably as a consequence of endothelial injury during cardiopulmonary bypass, precipitating right heart failure or even cardiac arrest. Intravenous or inhalational vasodilator drugs are the cornerstones in the management of these crises. In a study of 42 children after surgery for congenital heart disease, 7 required postoperative treatment with i.v. $PGI_2$ (5 to 10 ng · $kg^{-1}$ · $min^{-1}$) because of severe pulmonary hypertension. This caused pulmonary vasodilation, as evidenced by a reduction in mean pulmonary blood pressure and vascular resistance by 37 and 43% on average, even in patients who did not respond to tolazoline, the traditional treatment for such pulmonary hypertensive crises [86]. Additionally, prostacyclin was superior to other vasodilators (sodium nitroprusside, nifedipine, tolazoline) in reducing pulmonary blood pressure in 16 children with postoperative pulmonary hypertension [87].

However, in a more recent study in 13 children with severe pulmonary hypertension after cardiac surgery, inhaled NO reduced pulmonary artery pressure more than i.v. $PGI_2$ without causing systemic vasodilation [88]. Since only inhaled NO improved oxygenation, the authors concluded that this should be the drug of choice when treating patients with postoperative pulmonary hypertension.

In addition, our own experience derived from 3 patients with acute right ventricular failure associated with pulmonary hypertension after elective cardiac surgery suggests longer term inhalation of aerosolized $PGI_2$ for up to 2 weeks; we found sustained and reproducible decreases in pulmonary arterial pressure without signs of tachyphylaxis (unpublished observations).

Thus, it appears that $PGI_2$, either as an i.v. infusion or inhaled as an aerosol, is a viable treatment option to relieve pulmonary hypertension after cardiac surgery.

## Extracorporeal blood circulation procedures

Patients in need of extracorporeal blood circulation procedures to restore disturbed organ function (renal, pulmonary, or cardiocirculatory) often present with thrombocytopenia because of platelet damage and microemboli formation, despite conventional anticoagulation, both resulting in bleeding problems. In this context, $PGI_2$ has been suggested as an alternative or addition to standard anticoagulation regimens. Several studies using $PGI_2$ (at doses of 2.5–10 ng · $kg^{-1}$ · $min^{-1}$) in addition to or instead of heparin during renal hemodialysis, continuous venovenous hemofiltration, or cardiopulmonary bypass showed preservation of platelet numbers and function [89], with a reduction in blood loss [90–92] and no clinically important changes in measurements of the integrity of the intrinsic clotting system [93, 94]. Furthermore, administration of $PGI_2$ during hemodialysis or continuous hemofiltration significantly prolonged the duration of hemofilter function [95–97]. Since systemic hypotension as a consequence of vasodilation may be an undesired side effect [94], the patient's volume status should be monitored carefully. However, better hemodynamic profiles (i.e., no decrease in systemic and pulmonary arterial pressures) and enhanced hemofilter duration were achieved when $PGI_2$ and heparin were combined rather than given singly [95].

## Side effects and complications

The fact that $PGI_2$ is a potent vasodilator implies that several side effects are likely to be associated with i.v. use including systemic hypotension with subsequent ta-

chycardia (due to activation of the sympathetic nervous system through baroreceptors), in particular in hypovolemic patients, and an increased venous admixture causing hypoxemia. These effects might limit the use of $PGI_2$ in patients with septic shock or severe respiratory failure. Further common side effects include facial flushing, nausea and vomiting, headache, abdominal pain, and diarrhea, as shown in healthy volunteers [45], in patients undergoing hemodialysis [93, 94], and during long-term use of $PGI_2$ in patients with primary pulmonary hypertension [93]. However, these side effects are normally of minor relevance in sedated intensive care patients and are rapidly reversed (within 15 to 30 min) on stopping the infusion. None of these systemic side effects caused by the vasodilator action of $PGI_2$ have been reported when inhalation has been used. However, some investigators observed bronchoconstriction during $PGI_2$ inhalation (decrease in maximum expiratory flow and forced expiratory volume), despite protective activity against metacholine-provoked bronchoconstriction in subjects with mild allergic asthma [98]. Most important, there is at present no evidence for any toxic side effects on the airway epithelial cells during short-term inhalation [83], which is remarkable in view of the use of an alkaline buffer solution.

Because of its inhibitory effects on platelet aggregation, $PGI_2$, regardless of its route of delivery, usually prolongs cutaneous bleeding time and may increase the risk of bleeding, which might limit use in postoperative patients. However, there have been no reports about serious bleeding problems associated with $PGI_2$. Nevertheless, $PGI_2$ should not be used in patients with hemorrhagic diathesis, intracerebral bleeding or trauma, or in premature newborns ( < 35th week of gestation). Additionally, it should be used with caution when thrombocytopenia is present ( $< 80000\ \mu l^{-1}$), whereas it may be an alternative anticoagulant in heparin-induced thrombocytopenia and mechanical platelet destruction during extracorporeal procedures.

After abrupt discontinuation of $PGI_2$, there may be a substantial and rapid increase in systemic and pulmonary blood pressures. This sudden increase after stopping $PGI_2$ infusion can even rebound to values between 25 and 65 % above the preinfusion level [91, 99]. The associated transient cardiac dysfunction and severe dyspnea, however, seem not to be mediated by cyclooxygenase metabolites of arachidonic acid (e. g., $TX\ A_2$), since concurrent cyclooxygenase inhibition did not attenuate these responses in experimental pulmonary hypertension [99].

## Perspective

Most of the results of beneficial actions of $PGI_2$ stated above derive from studies employing short-term use in a limited number of patients. Therefore, the results are not predicative of any influence on patients' outcome. Consequently, controlled, randomized studies including larger populations, as well as outcome studies using longer term use of $PGI_2$, are necessary to determine which patients may benefit from $PGI_2$ infusion.

There are several diseases in which $PGI_2$ has been used successfully, which might have implications for intensive care medicine but are beyond the scope of this review. In patients with primary pulmonary hypertension, $PGI_2$ has been shown to improve both the quality and duration of patients' lives after longer term application [100]. In transplantation surgery, $PGI_2$ has been used successfully to dilate vessels in donor organs, as an additive to solutions for organ preservation, or in the treatment of perfusion abnormalities after organ transplantation. Furthermore, the salutary effects of $PGI_2$ on angina in patients with coronary artery disease should be mentioned [101] as well as its salutary effects in the management of severe heart failure, where $PGI_2$ increases cardiac output and reduces cardiac filling pressures. Finally, the numerous synthetic analogues of $PGI_2$ developed for special indications and the effects of other vasodilator prostaglandins like $PGE_1$ are not included in this review.

The inhalational route of $PGI_2$ delivery is a new and interesting application which can replace intravenous vasodilator therapy for pulmonary hypertension. In view of the similar efficacy but reduced toxicity compared to NO, inhalation of aerosolized $PGI_2$ may become a reasonable and safer alternative to NO inhalation in the selective treatment of pulmonary hypertension.

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