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Prostacyclin for the Treatment of Pulmonary Hypertension in the Adult Respiratory Distress Syndrome: Effects on Pulmonary Capillary Pressure and Ventilation–Perfusion Distributions

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Nine patients who had developed pulmonary artery hypertension during the adult respiratory distress syndrome (ARDS) were treated with an infusion of prostacyclin (PGI_2) (12.5–35.0 $ng \cdot kg^{-1} \cdot min^{-1}$). Whether PGI_2 might decrease the pulmonary capillary pressure (PCP) obtained by analysis of the pulmonary artery occlusion pressure decay curve and improve systemic oxygen delivery was examined. Gas exchange alterations induced by PGI_2 were analyzed by using the multiple inert gas elimination technique. PGI_2 reduced the pulmonary artery pressure from 35.6 to 28.8 mmHg ($P < 0.001$) and the PCP from 22.9 to 19.7 mmHg ($P < 0.01$) without changing the contribution of the pulmonary venous resistance to the total pulmonary vascular resistance. The cardiac index increased from 4.2 to 5.7 $l \cdot min^{-1} \cdot m^{-2}$ ($P < 0.001$) due to both increased stroke volume and heart rate. Despite a marked deterioration of ventilation–perfusion ($\dot{V}_A/\dot{Q}$) matching with increased true intrapulmonary shunt flow from 28.6% to 38.6% ($P < 0.01$) of the cardiac output, the Pa_{O_2} was unchanged due to increased mixed venous oxygen content indicated by an augmented mixed venous P_{O_2} (from 37.0 to 41.9 mmHg, $P < 0.01$). This caused a 35% ($P < 0.001$) increase of the systemic oxygen delivery rate. Thus, short-term infusions of PGI_2 reduced PAP and PCP without deleterious effects on arterial oxygenation in patients with ARDS. Hence, PGI_2 may be useful to lower pulmonary vascular pressures in patients with ARDS. (Key words: Lung, circulation: pulmonary capillary pressure; pulmonary hypertension. Ventilation–perfusion relationships: ARDS, prostacyclin.)

PULMONARY HYPERTENSION is a characteristic feature of the adult respiratory distress syndrome (ARDS),[1] its level being related to the severity of the lung injury[2] and the degree of pulmonary edema.[3] Reducing pulmonary vascular pressures is of importance in the management of patients with ARDS[4] because pulmonary hypertension fosters edema formation due to an increased pulmonary capillary pressure (PCP).[5] Treatment of pulmonary hypertension with vasodilators is currently under investigation. Infusion of prostaglandin E_1 or more conventional vasodilators, such as sodium nitroprusside or nitroglycerin, however, is reported to increase venous admixture with a concomitant decrease of Pa_{O_2}.[6–8]

Prostacyclin (PGI_2) has been successfully infused to decrease pulmonary artery pressure (PAP) in patients with primary pulmonary hypertension[9] and was reported not only to increase oxygen delivery in patients with septic acute respiratory failure but also to improve its distribution as documented by an augmented oxygen uptake.[10] Because pulmonary endothelium is injured in ARDS and PGI_2 produced by endothelial cells is a natural vasodilator and platelet aggregation inhibitor[11] with cytoprotective properties,[12] it should perhaps replace other drugs in the treatment of ARDS.

We tested the hypothesis that reducing pulmonary hypertension with PGI_2 might decrease the pulmonary capillary pressure and improve systemic oxygen delivery in patients with ARDS. To explain any gas exchange alterations caused by PGI_2 infusion, we studied its effects on the distributions of ventilation–perfusion ($\dot{V}_A/\dot{Q}$).

Methods

Nine consecutive patients with ARDS (table 1) without a history of previous lung disease and a compatible underlying pathology (table 1) who met common clinical and radiologic criteria for the diagnosis of ARDS were selected for this study. All patients were investigated within 48 h after the diagnosis of ARDS, and their lung injury was characterized according to scoring system ranging from 0 (normal) to a maximum of 4 points per criterion[13]: 1) a chest radiograph showing diffuse parenchymal opacities confined to at least three quadrants; 2) arterial hypoxemia defined as arterial oxygen partial pressure divided by inspiratory oxygen fraction below 299 mmHg ($Pa_{O_2}/FI_{O_2} < 299$ mmHg); 3) PEEP of at least 7 cmH_2O; and 4) a respiratory compliance defined as the tidal volume (V_T) divided by the difference between the end-inspiratory and the end-expiratory pressure below 70 ml/cmH_2O ($V_T/(P_{insp} - P_{exp}) < 70$ ml/cmH_2O). Converting these criteria into the lung injury score and subsequent division of the aggregate sum by the number of components yielded a median of 2.75 for our patients. All had pulmonary artery wedge pressures (PAWP) below

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TABLE 1. Clinical Characteristics of the Patients

Patient (no./Sex)	Age (yr)	Diagnosis	Outcome	FI_{O_2}	PEEP (cmH_2O)	Compliance (ml/cmH_2O)	Lung Failure Score
1/M	68	Multiple trauma: chest contusion, tibia and fibula fractures, cerebral contusion	Alive	0.48	10	38	2.75
2/M	61	Bowel perforation, peritonitis, sepsis	Alive	0.48	13	57	2.50
3/F	35	Hysterectomy plus radical lymphadenectomy, multiple transfusion, sepsis	Dead	0.64	8	24	2.75
4/M	64	Multiple trauma: chest contusion, cerebral contusion	Alive	0.39	12	53	2.50
5/M	25	Multiple trauma: chest contusion, tibia and fibula fractures, cerebral contusion	Alive	0.96	13	56	2.75
6/F	44	Pancreatitis, acute renal failure, sepsis	Dead	0.82	10	35	3.00
7/M	18	Multiple trauma: abdominal and chest contusion, femoral fracture	Alive	0.72	7	29	2.75
8/M	28	Aspiration pneumonia	Alive	0.99	12	67	2.75
9/F	32	Necrotizing pancreatitis	Dead	0.51	22	29	3.50
Mean				0.67	11.9	43.1	
SD				0.22	4.3	15.3	

18 mmHg and exhibited pulmonary hypertension with a mean PAP ≥ 28 mmHg. The patients' lungs were mechanically ventilated *via* an endotracheal tube using a volume-cycled ventilator (Servo 900 C, Siemens-Elema, Lund, Sweden) with tidal volumes of 14–17 ml/kg body weight, respiratory rates of 9–15 breaths/min, and 7–22 cmH_2O of PEEP. The mean FI_{O_2} was 0.67 (range 0.39–0.98). For monitoring and continuous pressure recording a thermodilution pulmonary artery catheter (model 93A-431H-7.5F, Edwards Laboratories Europe, Ternat, Belgium) and radial artery catheters were inserted. The patients were sedated with a continuous intravenous (iv) infusion of fentanyl and midazolam and paralyzed with intermittent doses of vecuronium. No other cardiotonic, vasoactive drugs, corticosteroids, or nonsteroidal antiinflammatory drugs were administered within 48 h of the study. The study protocol was approved by the local ethical committee.

The following measurements were obtained: 1) tidal volume and minute ventilation using an ultrasound spirometer (model VM 90, Bourns Inc., Riverside, California); 2) FI_{O_2} of a gas sample from the inspiratory limb of the ventilator (ABL 30, Radiometer, Copenhagen); 3) arterial (a) and mixed venous ($\bar{v}$) *p*H, P_{O_2}, and P_{CO_2} (ABL 30); total hemoglobin (Hb) and hemoglobin oxygen saturation (S_{O_2}) by spectrophotometry (OSM 2 Hemoximeter, Radiometer); 4) systemic and pulmonary vascular pressures (Combitrans transducers, Braun Melsungen, Melsungen, FRG); and 5) cardiac output using a thermodilution cardiac output computer (Edwards model REF-1), the values reported being the mean of eight injections of 10 ml 0° C saline at 0%, 25%, 50%, and 75% of the respiratory cycle (two injections at each fraction of the ventilatory cycle) using a pneumatically driven syringe triggered by the ventilator.[14] The pressure tracings and a continuous electrocardiogram (ECG) were recorded on a VP 95 recorder (Seikosha, Japan).

Systemic (SVRI) and pulmonary (PVRI) vascular resistance indices, oxygen delivery ($\dot{D}_{O_2}$) and uptake ($\dot{V}_{O_2}$) rates, and venous admixture ($\dot{Q}_{VA}/\dot{Q}_T$) were calculated by standard formulas.

The PCP was estimated by mathematical analysis of the pressure decay curve after pulmonary artery occlusion.[15] The difference (PAP − PAWP) is plotted on a semilogarithmic scale as a function of time, and the second, slow linear component is extrapolated to the time of pulmonary artery occlusion.[16] The pressure tracings were recorded after the endotracheal tube had been clamped at end-expiration to avoid respiratory artifact. The values reported are the mean of five analyses each with clearly distinguishable inflection points on the semilogarithmic pressure tracing. The coefficient of variation of the PCP assessment was 4.2%. In one patient (no. 6) no PCP data could be obtained because of distorted pressure tracings. The contribution of pulmonary venous resistance ($PVRI_{ven}/PVRI$) to the resistance of the whole pulmonary vasculature was calculated as the ratio between the pressure gradient over the venous bed (PCP − PAWP) and the total pressure drop (PAP − PAWP) across the lung.

Continuous $\dot{V}_A/\dot{Q}$ distributions were determined using the multiple inert gas elimination technique of Wagner *et al.*[17] as described previously.[8] Briefly, Ringer's lactate equilibrated with six inert gases (sulphur hexafluoride

(SF_6), ethane, cyclopropane, halothane, ether, and acetone) was infused into a peripheral vein. Arterial and mixed venous blood samples and mixed expiratory gas samples taken from a specially designed heated mixing box were analyzed for inert gases with a SiCHROMAT 1 gaschromatograph (Siemens, Cologne, FRG) equipped with a sample splitter and a flame ionization and an electron capture detector. The coefficient of variation of inert gas concentrations was 3.6% for SF_6 and 2.5–3.8% for the other five gases in subsequently obtained blood samples. Inert gas solubilities in blood were measured for each patient, and with these values inert gas partial pressure retention–solubility and excretion–solubility curves were constructed. Continuous $\dot{V}_A/\dot{Q}$ distributions for a 50-compartment lung model were computed using an appropriate algorithm,[18] and a computer-assisted analysis allowed estimation of true right-to-left shunt ($\dot{Q}_S/\dot{Q}_T$, *i.e.*, $\dot{V}_A/\dot{Q} < 0.005$), perfusion of low $\dot{V}_A/\dot{Q}$ ($0.005 < \dot{V}_A/\dot{Q} < 0.1$) and central $\dot{V}_A/\dot{Q}$ ($0.1 < \dot{V}_A/\dot{Q} < 10$) areas, and dead space ventilation ($\dot{V}_D/\dot{V}_T$, $\dot{V}_A/\dot{Q} > 100$). The mean residual sum of squares was 3.83 ± 3.39 indicating compatibility between the measured inert gas data and the calculated distributions.

Protocol

Two successive sets of measurements were obtained at levels of PEEP and FI_{O_2}, which were not changed from the maintenance values used before the study. Data were always collected after 30 min had elapsed with stable hemodynamic conditions. The control data acquisition took place 1 h before starting the PGI_2 infusion. PGI_2 was dissolved in a glycine buffer of *p*H 10.5 (10 μg/ml) and infused through a central venous catheter. The infusion rate was incrementally adjusted to achieve a 25% (range, 16–34%) decrease of systemic arterial pressure (SAP). Infusion rates of 12.5–35 ng/kg body weight were required to obtain this effect. After the PGI_2 infusion was discontinued hemodynamics returned to baseline values.

TABLE 2. Hemodynamic Responses to Treatment with PGI_2

	Control	PGI_2
HR (beats/min)	97.7 ± 15.9	114.0 ± 16.1*
SAP (mmHg)	87.8 ± 9.5	63.3 ± 6.9*
PAP (mmHg)	35.6 ± 5.5	28.8 ± 4.4*
RAP (mmHg)	14.6 ± 3.0	12.8 ± 2.4†
PAWP (mmHg)	17.6 ± 1.8	16.0 ± 1.5†
CI ($l \cdot min^{-1} \cdot m^{-2}$)	4.2 ± 1.3	5.7 ± 1.2*
SVI ($ml \cdot m^{-2}$)	42.0 ± 6.6	49.7 ± 5.3*
SVRI ($mmHg \cdot min \cdot m^2 \cdot l^{-1}$)	19.0 ± 6.9	9.6 ± 2.2*
PVRI ($mmHg \cdot min \cdot m^2 \cdot l^{-1}$)	5.1 ± 2.1	2.4 ± 0.9*

* $P < 0.001$, *versus* control.
† $P < 0.01$, *versus* control.

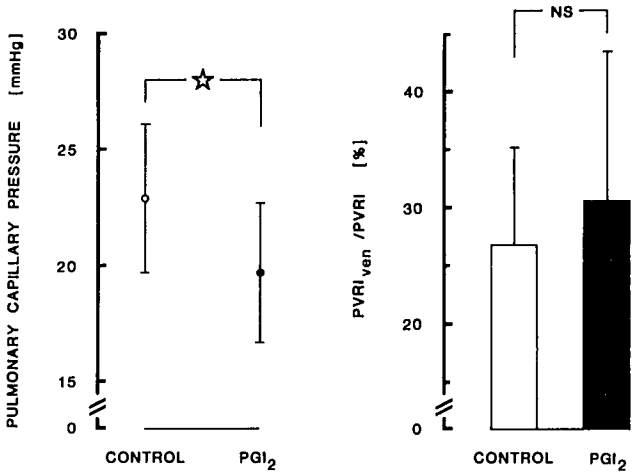

FIG. 1. Pulmonary capillary pressure (*left*) and the ratio of venous to total pulmonary vascular resistance (*right*) in the control period (open columns) and during PGI_2 infusion (shaded columns). All values are mean ± SD. *Significant difference between the control and PGI_2 infusion ($P < 0.01$).

Statistical Analysis

Paired data obtained before and during the PGI_2 infusion were compared with a nonparametric Wilcoxon rank-sign test for paired data. When a linear regression was calculated, the coefficient of correlation was tested using a *t* distribution.[19] Significance was assumed if $P < 0.05$.

Results

The hemodynamic effects of PGI_2 infusion and the control values are summarized in table 2. The reduction of the SAP was paralleled by a decreased PAP (from 35.6 ± 5.5 mmHg to 28.8 ± 4.4 mmHg, $P < 0.001$) as well as decreased RAP ($P < 0.01$) and PAWP ($P < 0.01$). The reduced pulmonary vascular pressures were associated with a significantly decreased PCP (from 22.9 ± 3.2 to 19.7 ± 3.0 mmHg, $P < 0.01$) (fig. 1).

Cardiac index (CI) rose from 4.18 ± 1.27 to 5.68 ± 1.22 $l \cdot min^{-1} \cdot m^{-2}$ ($P < 0.001$) during PGI_2 infusion due to an increase of heart rate with an augmented stroke volume index (SVI). The decreased pulmonary and systemic vascular pressures and the increased CI during PGI_2 infusion resulted in a considerable reduction of the SVRI as well as the PVRI. The mean contribution of the pulmonary venous resistance ($PVRI_{ven}/PVRI$) to the whole pulmonary vascular resistance was 0.27 ± 0.09 and did not change during PGI_2 infusion (fig. 1).

The oxygen exchange data are summarized in table 3. Despite a significant increase of $\dot{Q}_{VA}/\dot{Q}_T$, PGI_2 infusion did not significantly alter the Pa_{O_2}. Therefore, the increased CI was associated with increased $\dot{D}_{O_2}$ (from 649

TABLE 3. Oxygen Exchange in the Control Period and during PGI_2 Infusion

	Control	PGI_2
Pa_{O_2} (mmHg)	91.7 ± 21.4	86.3 ± 28.6
Pa_{CO_2} (mmHg)	41.9 ± 9.5	40.6 ± 9.0
$P\bar{v}_{O_2}$ (mmHg)	37.0 ± 4.3	41.9 ± 4.1*
$A\text{-}V_{\dot{D}O_2}$ (ml · 100 ml^{-1})	4.1 ± 0.9	3.0 ± 1.0*
$\dot{D}_{O_2}$ (ml · min^{-1} · m^{-2})	649 ± 166	872 ± 163†
$\dot{V}_{O_2}$ (ml · min^{-1} · m^{-2})	162 ± 21	167 ± 36
$\dot{Q}_{VA}/\dot{Q}_T$ (%)	29.3 ± 10.3	38.8 ± 11.0*

* $P < 0.01$, *versus* control.
† $P < 0.001$, *versus* control.

± 166 to 872 ± 163 ml · min^{-1} · m^{-2}, $P < 0.001$). Irrespective of this increased $\dot{D}_{O_2}$, we did not find an alteration of the calculated $\dot{V}_{O_2}$. This result was underscored by the increased mixed venous P_{O_2} ($P\bar{v}_{O_2}$). Arterial P_{CO_2} and *p*H values did not change during PGI_2 infusion.

Inert gas analysis demonstrated that the measured $\dot{Q}_{VA}/\dot{Q}_T$ values were either due to an increased right-to-left shunt alone ($\dot{Q}_S/\dot{Q}_T$) or to the combination of shunt and perfusion of lung regions with low $\dot{V}_A/\dot{Q}$ ratios. The latter ranged from 1.6% to 17.5% of total pulmonary blood flow (table 4). Infusing PGI_2 resulted in a significant increase of $\dot{Q}_S/\dot{Q}_T$ from 28.6 ± 10.7% to 38.6 ± 14.5% ($P < 0.01$), which was paralleled by a diminished perfusion fraction to central $\dot{V}_A/\dot{Q}$ compartments. A typical distribution of ventilation and perfusion in the control period and during PGI_2 infusion is presented in figure 2. The mean low $\dot{V}_A/\dot{Q}$ area perfusion fraction remained stable, although in four patients (nos. 1, 2, 4, and 9) the increased $\dot{Q}_S/\dot{Q}_T$ during drug infusion was accompanied by augmented perfusion of low $\dot{V}_A/\dot{Q}$ areas.

Discussion

Reducing the PAP is regarded[4,20] as an important part of the management of ARDS. In the present study we investigated the short-term effects of PGI_2 infusion upon central hemodynamics and pulmonary gas exchange. We chose PGI_2, a naturally occurring vasodilator produced by endothelial cells with antiplatelet aggregation[11] and cytoprotective abilities,[12] because endothelial injury with diffuse pulmonary vasoconstriction[2] and microthrombosis[21] are probable causes of pulmonary artery hypertension associated with ARDS.

The administration of PGI_2 induced a decrease in both the mean SAP and PAP associated with a 35% increase in CI, which was in part due to an increased SVI. An effect on left ventricular performance may have contributed to the increased CI and SVI in our patients: PGI_2 infusion induced a substantial decrease of the SVRI indicating a reduction of the left ventricular afterload together with a reduced PAWP, suggesting a reduced left ventricular preload. A similar effect of PGI_2 infusion on left ventricular performance has been reported in patients with congestive heart failure.[22]

The reduced pulmonary vascular pressures during PGI_2 infusion were associated with a mean reduction of 3.3 mmHg of the PCP. The reduced capillary hydrostatic pressure if it were maintained for a longer period should result in less pulmonary edema formation. In this short-term infusion study we did not measure extravascular lung water; therefore, we could not determine the effects of pulmonary vasodilation on fluid accumulation. It is likely that consistently lowering PCP by even a few millimeters of mercury will reduce microvascular filtration. Grimbert calculated that lowering the capillary pressure by 3 mmHg would reduce the filtration rate by a factor of 8 in dog lungs after acid aspiration.[23] A beneficial effect of PGI_2 infusion during acute lung injury has been demonstrated in awake sheep after the injection of thrombin. Reducing the PCP by 10 mmHg resulted in a 50% decrease of the pulmonary lymph flow with an unchanged lymph to plasma protein ratio.[24]

The mean contribution of the pulmonary venous resistance to the total pulmonary vascular resistance ($PVRI_{ven}/PVRI$) was 0.27, confirming results of a previous study[8] in a group of patients with mild and moderate ARDS in which a mean $PVRI_{ven}/PVRI$ ratio of 0.28 had been found. In a group of patients with more severe severe acute respiratory failure than in this study, Collee *et al.*[25] reported a ratio $PVRI_{ven}/PVRI$ of 0.47 using a computer to analyze the pressure decay. This difference and the higher PCP (33 ± 1 mmHg *vs.* 22.9 ± 3.2 mmHg in our study) may be due to the fact that, in contrast to the patients of Collee *et al.*,[25] in our patients all investigations were performed within 48 h after the onset of the disease, *i.e.*, in an early stage of ARDS when vasoconstriction is a major component of pulmonary hypertension.[2] This vasoconstriction is due to hypoxia and release of mediators, such as serotonin or thromboxane.[26] Because the site of action of hypoxia and most mediators as vasoconstrictor stimuli is the arterial segment,[27] the ratio $PVRI_{ven}/PVRI$ is likely to decrease when pulmonary hypertension is mainly due to vasoconstriction. The higher PCP values

TABLE 4. Inert Gas Data in the Control Period and during PGI_2 Infusion

	Control	PGI_2
$\dot{Q}_S/\dot{Q}_T$ (%)	28.6 ± 10.7	38.6 ± 14.5*
Low $\dot{V}_A/\dot{Q}$ (%)	4.0 ± 6.4	4.3 ± 5.6
Central $\dot{V}_A/\dot{Q}$ (%)	67.1 ± 15.3	56.9 ± 11.3†
$\dot{V}_D/\dot{V}_T$ (%)	26.2 ± 6.1	26.8 ± 8.7

* $P < 0.01$, *versus* control.
† $P < 0.001$, *versus* control.

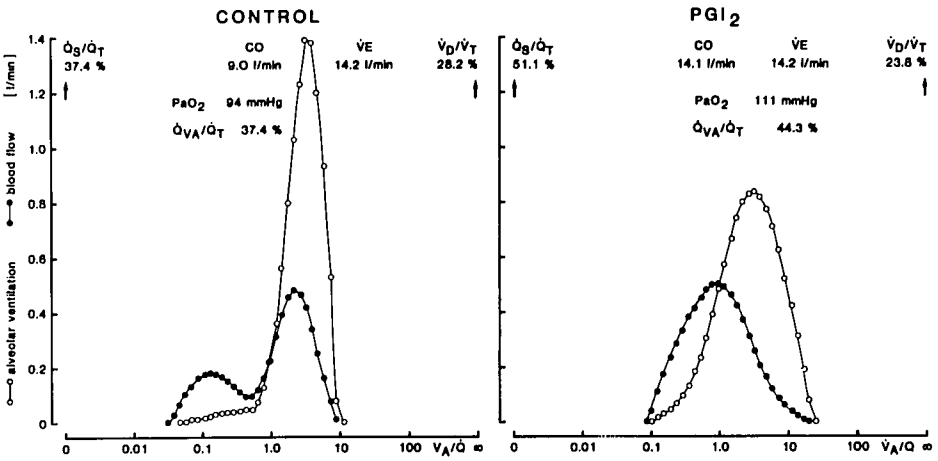

FIG. 2. Continuous distributions of ventilation (open circles) and perfusion (solid circles) in the control period (*left*) and during PGI_2 infusion (*right*). Despite the considerable increase of $\dot{Q}_s/\dot{Q}_t$, arterial P_{O_2} was even augmented due to the increased cardiac output. Note that the increased shunt flow was associated with the disappearance of the small perfusion fraction to lung areas with low $\dot{V}_A/\dot{Q}$ ratios.

in the patients of Collee *et al.*[25] are probably caused by the substantially higher levels of PAP (49 ± 10 mmHg *vs.* 35.6 ± 5.5 mmHg in our study) and PAWP (17.6 ± 1.8 mmHg *vs.* 27 ± 7 mmHg). For a given $PVRI_{ven}/PVRI$ ratio, higher upstream and downstream pressures in the pulmonary vasculature must yield a higher capillary pressure.

Systemic venous infusion of PGI_2 did not alter the $PVRI_{ven}/PVRI$ value. This lack of change during vasodilator infusion was similar to our previous study infusing prostaglandin E_1[8] and suggests that PGI_2 may act equally upon the arterial and venous pulmonary resistance without any predominating selective effect. This lack of selectivity has been shown for prostaglandins of the E series in animal experiments.[28] Despite the unchanged mean $PVRI_{ven}/PVRI$ ratio, the question of whether PGI_2 has a nonselective vasodilator effect on the pulmonary vasculature cannot be definitely settled. However, varying individual responses to the PGI_2 infusion were found inasmuch as $PVRI_{ven}/PVRI$ decreased in four patients, increased in three patients, and remained constant in one patient. Because of variable catheter position, the segment seen by the catheter does not necessarily represent the average lung pathology, especially in a heterogenously distributed lesion, such as in ARDS.[23]

As previously demonstrated for prostaglandin E_1,[6,7] the PGI_2 infusion increased the venous admixture. Inert gas analysis showed this increased $\dot{Q}_{VA}/\dot{Q}_T$ was due to an increased right-to-left shunt ($\dot{Q}_S/\dot{Q}_T$) and/or increased perfusion of lung regions with low $\dot{V}_A/\dot{Q}$ ratios. This was paralleled by a reduced perfusion fraction to normally ventilated lung areas (fig. 2). It is possible that this shift of the pulmonary perfusion is caused by the increase of either or both of the major determinants of $\dot{Q}_S/\dot{Q}_T$, *i.e.*, cardiac output[29] and $P\bar{v}_{O_2}$.[30] Whereas cardiac output may increase right-to-left shunt by promoting vascular recruitment in nonventilated units[31] or by increasing alveolar edema,[32] increased $P\bar{v}_{O_2}$ may cause shunt to increase due to inhibition of hypoxic vasoconstriction.[33] The duration of the PGI_2-induced variations in cardiac output are unlikely to have affected lung water. The effect of the increased $P\bar{v}_{O_2}$ on hypoxic vasoconstriction cannot be precisely evaluated because PGI_2 infusion itself inhibits hypoxic pulmonary vasoconstriction.[34]

We did not find any correlation between the change of either of the two parameters, cardiac output and $P\bar{v}_{O_2}$, and the change of the shunt flow. This result is probably due to the fact that despite the unchanged overall mean perfusion fraction to low $\dot{V}_A/\dot{Q}$ areas, each individual's response to PGI_2 infusion was variable. In three patients (nos. 1, 2, and 4) we observed the *de novo* appearance of perfusion to low $\dot{V}_A/\dot{Q}$ lung regions during PGI_2 infusion accounting for 16.4%, 8.9%, and 6.7% of the blood flow, respectively. In comparison, three other patients (nos. 5, 6, and 7) had a low $\dot{V}_A/\dot{Q}$ area perfusion fraction accounting for 5.4%, 11.9%, and 17.5%, respectively, of cardiac output during the control period, which virtually disappeared during PGI_2 infusion. Such an individually unpredictable response to a therapeutic intervention was already demonstrated by Ralph *et al.* in patients with ARDS.[35] They reported that ventilation at varying levels of PEEP resulted in varying perfusion distribution patterns.

The results from this study of PGI_2 contrasts with those from our previous study in which prostaglandin E_1 (PGE_1) was infused because the markedly increased $\dot{Q}_S/\dot{Q}_T$ was not associated with a reduced Pa_{O_2}. This difference is due to the greater effect of PGI_2 infusion on cardiac output and was also recently demonstrated by Prielipp *et al.*[36] in an ovine model of acute pulmonary hypertension. After producing equivalent reductions of the SAP they reported that PGI_2 infusion induced the largest increase of cardiac index compared with PGE_1 or nifedipine. In our patients PGI_2 induced a mean 35% increase of cardiac index lead-

ing to an increase of $P\bar{v}_{O_2}$ by 4.9 mmHg. This enhanced oxygen content entering the lung compensated for the increase of $\dot{Q}_S/\dot{Q}_T$ caused by PGI_2, resulting in a nearly unchanged Pa_{O_2} and arterial oxygen content.

Because the overall mean Pa_{O_2} was not altered during PGI_2 infusion, the considerable increase of cardiac index resulted in a markedly increased oxygen delivery ($\dot{D}_{O_2}$). Irrespective of this effect on $\dot{D}_{O_2}$, the overall mean calculated systemic oxygen uptake ($\dot{V}_{O_2}$) was not changed. This result is similar to a recent study by Annat *et al.*[37] who reported unchanged values of $\dot{V}_{O_2}$ in ARDS patients with normal blood lactate concentrations when $\dot{D}_{O_2}$ was decreased by increasing the level of PEEP. In their patients and in ours, $\dot{D}_{O_2}$ levels were $\geq 11 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and did not decrease below values of approximately 8 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The $\dot{D}_{O_2}$ levels in both studies are lower than the critical oxygen delivery threshold reported for patients with ARDS and below which a further reduction of $\dot{D}_{O_2}$ produces a proportional decrease of $\dot{V}_{O_2}$.[38] The absence of metabolic acidosis, however, suggests that little oxygen debt was present in our patients, making an increase of oxygen uptake unlikely due to increased oxygen delivery.

It has to be noted that in the two septic patients who subsequently died (nos. 3 and 6) increased $\dot{D}_{O_2}$ was associated with increased $\dot{V}_{O_2}$. This result is in accordance with data recently published by Bihari *et al.*,[10] who infused PGI_2 in a group of patients with septic ARF. In the nonsurvivor group the increased $\dot{D}_{O_2}$ induced an increased $\dot{V}_{O_2}$, whereas unchanged $\dot{V}_{O_2}$ was noted in the survivors.

In conclusion, short-term administration of PGI_2 attenuates pulmonary artery hypertension and lowers PCP in patients with ARDS. Although pulmonary vasodilation by PGI_2 is associated with an increased $\dot{Q}_{VA}/\dot{Q}_T$ due to a marked deterioration of $\dot{V}_A/\dot{Q}$ matching, PGI_2 infusion, in contrast to conventional vasodilators, did not reduce Pa_{O_2} probably because the markedly increased CI provided augmented tissue oxygen delivery. Because improving oxygen availability should be a major goal of the therapeutic management of patients with ARDS,[39] PGI_2 could be a useful drug; also, lower pulmonary vascular pressures are provided. Further investigation is warranted of long-term PGI_2 administration to improve survival of these patients.

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