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Prostacyclin and right ventricular function in patients with pulmonary hypertension associated with ARDS*

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Abstract. Eight patients who developed pulmonary artery hypertension during the adult respiratory distress syndrome (ARDS) were treated with an infusion of prostacyclin (PGI_2, 12.5–35.0 $ng \cdot kg^{-1} \cdot min^{-1}$) for 45 min. We examined whether reducing the right ventricular (RV) outflow pressures by PGI_2 infusion would increase the right ventricular ejection fraction (RVEF) measured by thermodilution. PGI_2 reduced the pulmonary artery pressure (PAP) from 35.6 to 29.1 mmHg ($p<0.01$). The cardiac index (CI) increased from 4.2 to 5.8 $l \cdot min^{-1} \cdot m^{-2}$ ($p<0.01$) partly due to an increased stroke volume. The decreased PAP together with the increased CI resulted in a fall of the calculated pulmonary vascular resistance index (PVRI, from 5.1 to 2.5 $mmHg \cdot min \cdot m^2 \cdot l^{-1}$, $p<0.01$). In the patients with subnormal baseline RVEF the increased stroke volume was associated with an increased RVEF (from 47.6% to 51.8%, $p<0.05$) suggesting improved RV function. This result was underscored by a significant relationship between the changes in PVRI and RVEF ($r=0.789$, $\Delta\%$ RVEF $= -2.11 \cdot \Delta PVRI - 1.45$). Despite an increased venous admixture from 27.8% to 36.9% ($p<0.05$) the arterial PO_2 remained constant resulting in an increased oxygen delivery from 657 to 894 $ml \cdot min^{-1} \cdot m^{-2}$ ($p<0.01$). We conclude that short term infusions of PGI_2 increased CI concomitant to improved RV function parameters when baseline RVEF was depressed. Since improved oxygen availability should be a major goal in the management of patients with ARDS PGI_2 may be useful to lower pulmonary artery pressure in ARDS.

Key words: ARDS – Pulmonary hypertension – Right ventricular function – Right ventricular ejection fraction – Thermodilution – Prostacyclin

Acute pulmonary hypertension (PH) is a characteristic feature of the adult respiratory distress syndrome (ARDS) [1], its level being related to the severity of the microvascular injury [2]. This PH may promote right ventricular (RV) dysfunction [3] possibly leading to a depression of forward flow due to an additional effect reflecting ventricular interdependence [4]. As unloading the right ventricle might improve RV function [5] vasodilator treatment of PH has been advocated. Infusing prostaglandin E_1 [6] or conventional vasodilators such as sodium nitroprusside [7], however, has failed to improve global RV function in patients with ARDS.

Recently, prostacyclin (PGI_2) has been successfully infused to lower the pulmonary artery pressure in patients with primary pulmonary hypertension [8] and was reported not only to increase systemic oxygen delivery but also to improve its distribution in patients with septic acute respiratory failure [9]. PGI_2 is a naturally occurring vasodilator produced by endothelial cells with antiplatelet aggregating abilities [10]. Since diffuse vasoconstriction [2] and microembolism [11] are putative mechanisms of PH associated with ARDS PGI_2 may be of benefit as a vasodilator. We tested the hypothesis that reducing PH with PGI_2 would improve RV function, as assessed by the thermodilution ejection fraction, and increase systemic oxygen delivery in patients with ARDS.

Patients and methods

Eight consecutive patients with no history of previous lung disease but a compatible underlying pathology (Table 1) who met common clinical and radiological criteria for ARDS were investigated within 48 h after the onset of the disease. Their lung injury was characterized according to a scoring system ranging from 0 (normal) to a maximum of 4 points per criterion [12]: 1) a chest radiograph showing diffuse parenchymal opacities confined to at least three quadrants; 2) arterial hypoxaemia defined $PaO_2/FiO_2 < 299$ mmHg; 3) a PEEP level of at least 8 cmH_2O.

Converting these criteria into the lung injury score and subsequent division by the aggregate number of components yielded a mean of 2.96±0.37 for our patients. All patients had pulmonary artery wedge

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Table 1. Clinical characteristics of the patients

Patient No/sex	Age (years)	Diagnosis	Outcome	FiO_2	PEEP level cmH_2O	Lung failure score
1/M	68	Multiple trauma: chest contusion, leg fractures, cerebral contusion	Alive	0.48	10	2.67
2/M	61	Bowel perforation, peritonitis, sepsis	Alive	0.48	13	2.67
3/F	35	Hysterectomy, radical lymphadenectomy, polytransfusion, sepsis	Dead	0.64	8	2.67
4/M	64	Multiple trauma: chest contusion cerebral contusion	Alive	0.39	12	2.67
5/M	25	Multiple trauma: chest contusion, leg fractures, cerebral contusion	Alive	0.96	13	3.00
6/M	44	Pancreatitis, acute renal failure, sepsis	Dead	0.82	10	3.00
7/M	28	Aspiration pneumonia	Alive	0.99	12	3.33
8/F	32	Necrotizing pancreatitis	Dead	0.51	22	3.67
			Mean	0.66	12.5	2.96
			SD	0.23	4.2	0.37

pressures (PAWP) below 18 mmHg [13] at zero end-expiratory pressure and exhibited pulmonary hypertension with a mean pulmonary artery pressure (PAP) equal to or greater than 28 mmHg. Patients were mechanically ventilated using a volume-cycled ventilator (Sero 900 C, Siemens Elema, Lund, Sweden) with tidal volumes of 14–17 ml/kg body weight, respiratory rates of 9–15 breaths min and 8–22 cmH_2O of PEEP. Their mean FiO_2 was 0.66 (range 0.39 to 0.99). A pulmonary artery catheter with a fast response thermistor (50 ms) and a modified port ending (model 93A–431H–7.5F, Edwards Laboratories Europe, Santa Ana, CA) and a radial artery catheter were placed for routine clinical haemodynamic monitoring. The patients were sedated with continuous infusions of fentanyl and midazolam and paralyzed with intermittent doses of vecuronium. No other cardiotonic or vasoactive drugs were administered throughout the study period. All patients had a normal sinus rhythm. No patient had evidence for tricuspid regurgitation from clinical examination or right atrial pressure curve analysis. The study protocol was approved by the local ethical committee, and the study was conducted according to the principles embodied in the Declaration of Helsinki.

The following measurements were obtained: 1) PiO_2 of a gas sample from the inspiratory limb of the ventilator (ABL 30, Radiometer, Copenhagen); 2) arterial (a) and mixed venous ($\bar{v}$) pH, PO_2 and PCO_2 (ABL 30); 3) total hemoglobin (Hb) and hemoglobin oxygen saturation (SO_2) by spectrophotometry (OSM 2 Hemoximeter, Radiometer). Vascular pressures and a continuous electrocardiogramm (ECG) were recorded on a VP 95 recorder (Seikosha, Japan), the values reported being obtained at end expiration with therapeutic PEEP levels. Cardiac index (CI) and right ventricular ejection fraction (RVEF) were assessed using a thermodilution cardiac output computer (Edwards model REF–1) with an algorithm based upon a new exponential curve analysis [14]. Each CI and RVEF value reported is 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 [15]. This techniques allowed us to compensate for cyclic modulations of RVEF due to mechanical ventilation [16]. The coefficient of variation (mean/standard deviation · 100) of the mean RVEF value over the whole ventilatory cycle taken together was 9.8%. The difference between the two respective measurements at one definite fraction of the respiratory cycle did not exceed 0.02 (2%), i.e. it remained below 7% of the mean of these two measurements [17]. As in a previous report [18] an RVEF change of 0.03 (3%) was considered a significant response to PGI_2 infusion.

The right ventricular end diastolic volume index (RVEDVI) was calculated using the RVEF, CI and the heart rate (HR) obtained by intracardiac ECG recording by the formula:

$$RVEDVI = CI \cdot HR^{-1} \cdot RVEF^{-1}.$$

Right ventricular coronary driving pressure (RVCDP) was calculated as the difference between the systolic arterial and RV pressures [19]. Levels of systemic (SVRI) and pulmonary (PVRI) vascular resistance indexes, systemic oxygen delivery ($\dot{D}O_2$) and uptake ($\dot{V}O_2$) and venous admixture ($\dot{Q}_{VA}/\dot{Q}_T$) were calculated by standard formulae:

$$SVRI = (SAP - RAP) \cdot CI^{-1},$$

$$PVRI = (PAP - PAWP) \cdot CI^{-1},$$

$$\dot{D}O_2 = CaO_2 \cdot CI,$$

$$\dot{V}O_2 = (CaO_2 - C\bar{v}O_2) \cdot CI,$$

$$\dot{Q}_{VA}/\dot{Q}_T = (CcO_2 - CaO_2) \,/\, (CcO_2 - C\bar{v}O_2),$$

where SAP is mean systemic arterial pressure, RAP right atrial pressure, and CaO_2, $C\bar{v}O_2$ and CcO_2 arterial, mixed venous and ideal end-capillary oxygen content. The oxygen content values were computed as $Hb \cdot 1.34 + PO_2 \cdot 0.0031$. CcO_2 was calculated as $Hb \cdot 1.34 + PAO_2 \cdot 0.0031$ with the PAO_2 derived from the alveolar gas equation and the directly measured PiO_2 assuming a respiratory quotient of 0.8.

Protocol

Two successive sets of measurements were obtained at levels of PEEP and FiO_2 which were not changed from the maintenance values used before the study. Data were always collected after 30 min had elapsed with stable haemodynamic conditions. The control data aquistion took place 1 h before starting the PGI_2 infusion. PGI_2 was dissolved ($10\,\mu g \cdot ml^{-1}$) in a glycine buffer of pH 10.5 and infused into a central venous catheter. The infusion rate was incremented to achieve a 25% (range 16%–34%) decrease of SAP. Infusion rates of $12.5–35\,ng \cdot kg^{-1} \cdot min^{-1}$ were required to obtain this effect. It was assured that after discontinuing the PGI_2 infusion SAP and PAP as well as RAP and PAWP were exactly the same as the baseline values.

Paired differences obtained before and during the PGI_2 infusion were compared with the non-parametric Wilcoxon rank-sign test for paired data [20]. When a linear regression was calculated, the coefficient of correlation (r) was tested using a t distribution [20]. Significance was assumed if the p value was below 0.05.

Results

The hemodynamic effects of PGI_2 and the control values are summarized in Table 2. The reduction of SAP during PGI_2 infusion was paralleled by a fall in mean PAP from 35.6 ± 5.9 to 29.1 ± 4.5 mmHg ($p < 0.01$) resulting in a fall of RVCDP ($p < 0.05$) and reduced RAP ($p < 0.05$) and PAWP ($p < 0.05$). CI increase from 4.2 ± 1.4 to $5.8 \pm 1.3\,l \cdot min^{-1} \cdot m^{-2}$ ($p < 0.01$) due to an elevated HR rising from 97 ± 17 to $115 \pm 17\,min^{-1}$ ($p < 0.05$) and an augmented stroke volume index (SVI) rising from

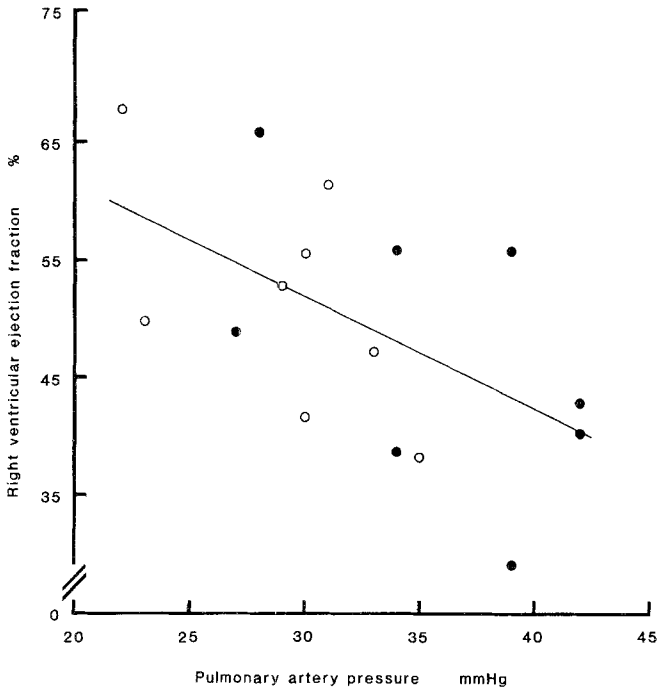

Fig. 1. Relationship between mean pulmonary artery pressure (PAP) and right ventricular ejection fraction (RVEF). *Solid circles* are values in the control period while *open circles* are data during PGI_2 infusion. The coefficient of correlation is $r = 0.549$ with the regression equation being % RVEF = $-0.97 \cdot PAP + 81.1$ ($p < 0.05$)

Table 2. Hemodynamic responses to treatment with PGI_2. HR heart rate, SAP mean systemic arterial pressure, PAP mean pulmonary artery pressure, RAP right atrial pressure, PAWP pulmonary artery wedge pressure, RVCDP right ventricular coronary driving pressure, CI cardiac index, SVI stroke volume index, SVRI systemic vascular resistance index, PVRI pulmonary vascular resistance index. All data are mean ± standard deviation. Asterisks denote significant differences between measurements during PGI_2 ingusion and the control period (*$p < 0.05$, **$p < 0.01$)

	Control	PGI_2
HR min^{-1}	97.9±17.0	115.0±16.9**
SAP mmHg	88.1±10.1	63.8±7.2**
PAP mmHg	35.6±5.9	29.1±4.5**
RAP mmHg	14.6±3.2	13.0±3.0*
PAWP mmHg	17.6±1.9	16.0±1.7*
RVCDP mmHg	85.8±18.7	70.8±18.0*
CI $l \cdot min^{-1} \cdot m^{-2}$	4.2±1.4	5.8±1.3**
SVI $ml \cdot m^{-2}$	42.0±7.1	49.9±5.6**
SVRI $mmHg \cdot min \cdot m^2 \cdot l^{-1}$	19.2±7.4	9.6±2.3**
PVRI $mmHg \cdot min \cdot m^2 \cdot l^{-1}$	5.1±2.2	2.5±1.0**

42.0±7.1 to 49.9±5.6 $ml \cdot m^{-2}$ ($p < 0.05$). The decreased pulmonary and systemic arterial pressures together with the increased CI during PGI_2 infusion resulted in a marked reduction of SVRI ($p < 0.01$) as well as of PVRI ($p < 0.01$).

A significant relationship was found between RVEF and PAP, the coefficient of correlation being $r = -0.549$ ($p < 0.05$) with the regression equation being % RVEF = $-0.97 \cdot PAP + 81.1$ (Fig. 1). PGI_2 infusion induced a small but significant increase of the overall mean RVEF from 47.6%±11.8% to 51.8%±9.8% ($p < 0.05$) for all patients together with no alteration of RVEDVI (Fig. 2). The mean change of RVEF was 6.8% for the patients with RVEF values below the normal range in the control period (nos. 1, 5, 7, 8), while it was 1.6% for those (nos. 2, 3, 4, 6) with RVEF values within the normal range. In each individual patient the mean change of RVEF over the entire ventilatory cycle was similar to those at each fraction of the respiratory cycle where thermodilution curves had been obtained. There was a significant relationship between the changes of RVEF and the

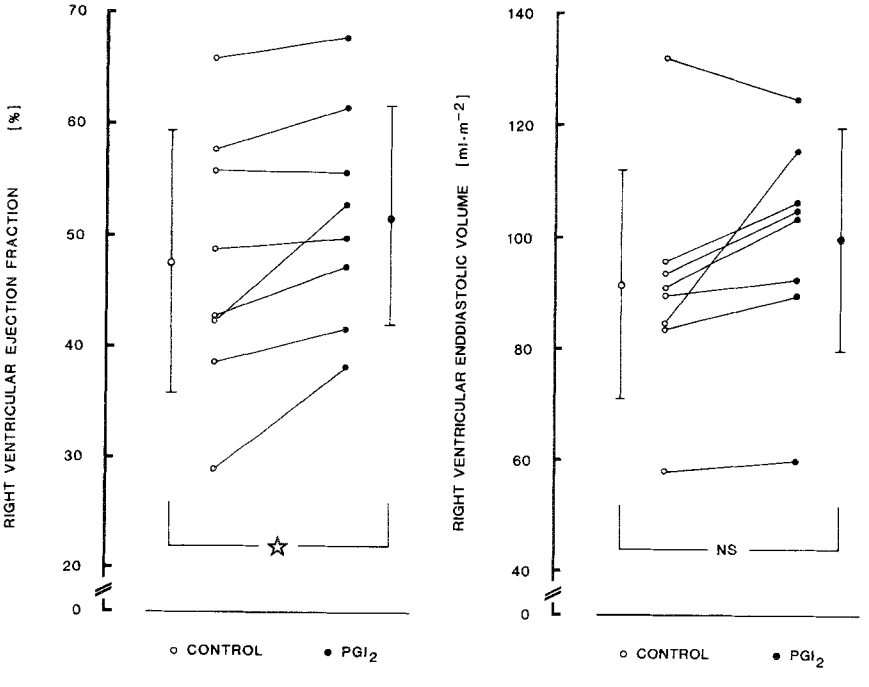

Fig. 2. Individual (*small solid circles*) and overall mean (*big solid circle*) responses of right ventricular ejection fraction (*left*) and right ventricular enddiastolic volume index (*right*) to PGI_2 infusion. The mean values are presented ± standard deviation, and the asterisk denotes a significant difference between the control period and PGI_2 infusion ($p < 0.05$)

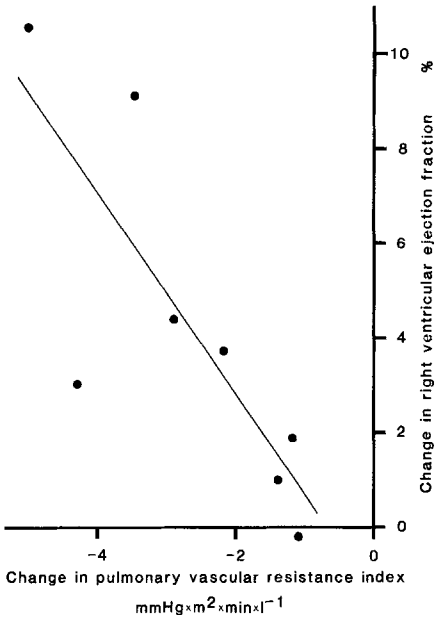

Fig. 3. Relationship between the changes in pulmonary vascular resistance index (PVRI) and change in right ventricular ejection fraction (RVEF) induced by PGI_2 infusion. The coefficient of correlation is $r = 0.789$ with the regression equation being $\Delta\%$ RVEF $= -2.11 \cdot \Delta$PVRI -1.45 ($p < 0.05$)

changes of PVRI, the coefficient of correlation being $r = 0.789$ ($p < 0.05$) with the regression equation being

$$\Delta\%\,\text{RVEF} = -2.11 \cdot \Delta\,\text{PVRI} - 1.45 \text{ (Fig. 3).}$$

Table 3 shows the oxygen exchange data in the control phase and during PGI_2 infusion. Despite a marked increase of $\dot{Q}_{VA}/\dot{Q}_T$ from 27.8 ± 9.9 to $36.9 \pm 10.0\%$ ($p < 0.01$) the PGI_2 infusion did not significantly alter the PaO_2. Therefore the increased CI was associated with an increase in $\dot{D}O_2$ from 657 ± 175 to $893 \pm 160\,\text{ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ($p < 0.01$). Irrespective of this increased $\dot{D}O_2$ we did not find any alteration of the calculated $\dot{V}O_2$. No changes were found for $PaCO_2$ or pH.

Discussion

Reducing pulmonary artery hypertension is regarded as an important component of the management of patients with ARDS. In this study we examined the question of whether decreasing PAP by short term infusions of PGI_2 would improve RV function as assessed by thermodilution RVEF. All our patients exhibited pulmonary artery hypertension and decreased global RV function could be anticipated. In fact, in four of the eight patients we measured RVEF values below the normal range of 45–65% [5] for the thermodilution technique, and a negative correlation was noted between RVEF and mean PAP. The latter result reproduces data reported by Sibbald and coworkers on the measurement of RVEF by gated radionuclide angiography [3]. These authors had observed a similar relationship between mean PAP and RVEF.

The administration of PGI_2 decreased both the mean PAP and the calculated PVRI. This effect was associated with a 38% increase of CI. Since the increased heart rate accounted for only half of the increase of CI, the other half resulted from a augmented stroke volume index (SVI). This increased SVI together with the increased RVEF suggested improved global RV function. This result is underscored by the significant relationship between the changes of RVEF and those of PVRI: a major reduction in one of the determinants of RV afterload was correlated with an increase in RV ejection fraction. Further support for the assumption that reducing RV outflow pressures by infusion of PGI_2 improves RV function is provided by the unchanged RV end diastolic volume index (RVEDVI) which was associated with a decreased RAP. These data suggest that PGI_2 infusion induced a change in the end diastolic pressure/volume relationship of the RV. Similar data have been reported by Vincent and coworkers when replacing dopamine by dobutamine in a group of critically ill patients [18]: a fall of the RAP was associated with unchanged RVEDVI. Several phenomena may have lead to this apparently improved RV compliance: A reduction of the RV end diastolic pressure documented by the fall in RAP could reduce RV wall tension and facilitate RV filling due to the decreased intrapericardial pressure [21]. This could result in improved left ventricular compliance with decreased LV filling pressures [21] as is suggested by the reduced PAWP in our patients.

A direct effect of PGI_2 infusion of left ventricular function has certainly contributed to the rise in CI in our patients as well. PGI_2 administration induced a substantial decrease in the SVRI indicating a reduction in the left ventricular afterload. This was true for the patients with normal and subnormal baseline RVEF values alike. Such an unloading effect of PGI_2 on the left ventricle has already been demonstrated by Yui and coworkers in patients with congestive heart failure [22].

We can only speculate whether the above mentioned putative reduction of RV wall tension was accompanied by improved RV coronary flow, in particular since RV coronary driving pressure was significantly reduced during PGI_2 infusion. It has to be noted, however, that RVCDP did not fall below 50 mmHg in any of our pa-

Table 3. Oxygen exchange data in the control period and during PGI_2 infusion. PaO_2 arterial oxygen partial pressure, $P\bar{v}O_2$ mixed venous oxygen partial pressure, $a\text{-}\bar{v}DO_2$ arterial-mixed venous oxygen content difference, $\dot{D}O_2$ oxygen delivery, $\dot{V}O_2$ calculated oxygen uptake, $\dot{Q}_{VA}/\dot{Q}_T$ venous admixture. All values are mean ± standard deviation. Asterisks denote significant differences between the control period and PGI_2 infusion (*$p < 0.05$, **$p < 0.01$)

	Control	PGI_2
PaO_2 mmHg	94.0 ± 21.7	89.8 ± 28.5
$P\bar{v}O_2$ mmHg	37.2 ± 4.6	42.5 ± 3.9*
$a\text{-}\bar{v}DO_2$ ml·100 ml^{-1}	4.2 ± 0.9	3.1 ± 1.0*
$\dot{D}O_2$ ml·min^{-1}·m^{-2}	6570 ± 175	894 ± 160**
$\dot{V}O_2$ ml·min^{-1}·m^2	1660 ± 20	172 ± 34
$\dot{Q}_{VA}/\dot{Q}_T$ %	27.8 ± 9.9	36.9 ± 10.0*

tients. In an animal model of acute right ventricular hypertension this level of RVCDP was associated with increased myocardial blood flow and was about twice as high as RVCDP levels which were accompanied by biochemical signs of RV free wall ischemia [23].

The change of the mean RVEF gained statistical significance although the overall mean for all patients together was only 4.2%. This relatively small difference was detectable because we used an automatic phase-selected pump injection triggered by the ventilator for the determination of the thermodilution curves [15]. Such a technique substantially improves the reproducibility of a single measurement [16, 17] and analysing mean differences becomes less sensitive to random measurement errors. Moreover, it has to be noted that in each individual patient the mean change of RVEF for the entire ventilatory cycle taken together was similar to the difference obtained at each separate fraction of the respiratory cycle where injections had been performed.

When looking at the individual responses to the PGI_2 infusion (Fig. 2) two distinct groups of patients can be identified: In the patients who exhibited pathologically low RVEF values in the control period (RVEF < 45%) [5] the mean increase in RVEF was 6.8%. This number exceeds the limit which is considered to be a significant response to RVEF to a therapeutic intervention for both the thermodilution [18] and radionuclide techniques [7]. In contrast the response in the four patients with normal baseline RVEF values was a mean change of RVEF of 1.6%. Three of these patients (nos. 2, 4, 6) had only slight alterations in RVEF. These particular data suggest that a normal baseline RVEF makes further increase due to PGI_2 infusion unlikely to occur. These observations reproduce results of our previous study of infusing prostaglandin E_1 in patients with moderate ARDS [6]; having achieved similar systemic arterial pressure effects, no change in RVEF was found during the drug infusion when the control values had been within the normal range.

Our result that PGI_2 infusion may enhance RVEF, evidence for improved global RV function, is in contrast to data reported after infusing sodium nitroprusside (SNP) in patients with ARDS [7]. Any differences may be due to a difference in severity of acute lung injury in that study compared to our own: although in the paper of Sibbald and coworkers the patients had a similar degree of pulmonary hypertension as our patients they had less impairment of gas exchange (mean $\dot{Q}_{VA}/\dot{Q}_T$ 20 ± 6 versus 27.8 ± 9.9% at PEEP levels of 8 ± 5 versus 12.5 ± 4.2 cm H_2O in our patients) indicating less severe lung injury. Moreover, there may be different microvascular vasodilator activity of SNP compared with PGI_2: while PGI_2 has been reported to increase oxygen delivery and improve its distribution in patients with septic acute respiratory failure [9], SNP may have deleterious effects upon the systemic microcirculation as demonstrated by intravital microscopy in hamsters [24]. Furthermore, PGI_2 has been reported to be superior to SNP after cardiopulmonary bypass or in children with septic shock [25].

A major concern surrounding vasodilator treatment in patients with ARDS is the question whether a possibly increased CI is associated with enhanced DO_2 since vasodilating drugs generally impair gas exchange [26, 27] which may result in a decreased DO_2 even when CI is increased [2]. In our patients PGI_2 infusion did not alter PaO_2 despite the increased $\dot{Q}_{VA}/\dot{Q}_T$; the considerable rise in CI lead to an increased mixed venous PO_2, and this increase in oxygen content entering the lung compensated for the rise in $\dot{Q}_{VA}/\dot{Q}_T$ resulting in unchanged PaO_2. Hence increased $\dot{D}O_2$ was measured in all patients. This finding confirms a previous study of infusing prostaglandin E_1 in patients with ARDS [27] and reproduces results recently reported by Bihari and coworkers [9]: both drugs induced a rise in $\dot{D}O_2$ despite a deterioration of gas exchange.

In summary, our data confirm that patients with ARDS complicated by pulmonary hypertension may exhibit depressed RV function as assessed by thermodilution RVEF. Reducing the RV outflow pressures with PGI_2 considerably increased CI which was partly due to enhanced RVEF when baseline RVEF was subnormal. Since this increased CI was not associated with a fall of PaO_2 it resulted in improved $\dot{D}O_2$. Improving oxygen availability and reducing pulmonary vascular pressures should be major goals of the therapeutic management of patients with ARDS since 1) these patients exhibit disturbed tissue oxygen extraction [28] with increased levels of critical oxygen delivery [29], and 2) reducing PAP decreases microvascular filtration [30] due to decreased capillary hydrostatic pressure [31]. Therefore PGI_2 may be a drug of choice when lower pulmonary artery pressures are sought in such a group of patients.

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