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Dose-Response to Inhaled Aerosolized Prostacyclin for Hypoxemia Due to ARDS*

P. Vernon van Heerden, MD; Anne Barden, PhD; Nicholas Michalopoulos, BSc; Max K. Bulsara, MSc; and Brigit L. Roberts, RN

Study objectives: **This study was carried out to determine the efficacy of and dose-response relationships to inhaled aerosolized prostacyclin (IAP), when used as a selective pulmonary vasodilator (SPV) in patients with severe hypoxemia due to ARDS.**
Design: **Unblinded, interventional, prospective clinical study.**
Setting: **A general ICU in a university-affiliated, tertiary referral center.**
Patients: **Nine adult patients with severe ARDS (lung injury score, ≥ 2.5).**
Interventions: **All patients received IAP over the dose range 0 to 50 ng/kg/min. The IAP was delivered via a jet nebulizer placed in the ventilator circuit. Dose increments were 10 ng/kg/min every 30 min.**
Measurements and results: **Cardiovascular parameters (cardiac index and mean pulmonary and systemic pressures), indexes of oxygenation (Pao_2/fraction of inspired oxygen [FIO_2] ratio and alveolar-arterial oxygen partial pressure difference [$P(A\text{-}a)O_2$]) and shunt fraction were measured or calculated at each dose interval, as were platelet aggregation and systemic levels of prostacyclin metabolite (6-keto prostaglandin $F1_\alpha$). A generalized linear regression model was used to determine a dose effect of IAP on these parameters. The Wilcoxon rank sum test for related measures was used to compare the effects of various doses of IAP. IAP acted as an SPV, with a statistically significant dose-related improvement in Pao_2/FIO_2 ratio ($p = 0.003$) and $P(A\text{-}a)O_2$ ($p = 0.01$). Systemic prostacyclin metabolite levels increased significantly in response to delivered IAP ($p = 0.001$). There was no significant dose effect on systemic or pulmonary arterial pressures, or on platelet function, as determined by platelet aggregation in response to challenge with adenosine diphosphate.**
Conclusions: **IAP is an efficacious SPV, with marked dose-related improvement in oxygenation and with no demonstrable effect on systemic arterial pressures over the dose range 0 to 50 ng/kg/min. Despite significant systemic levels of prostacyclin metabolite, there was no demonstrable platelet function defect.** ***(CHEST 2000; 117:819–827)***

Key words: aerosolized prostacylin; ARDS

Abbreviations: APACHE = acute physiology and chronic health evaluation; CI = cardiac index; CO = cardiac output; FIO_2 = fraction of inspired oxygen; IAP = inhaled aerosolized prostacyclin; 6-ketoPGF1_α = 6-keto prostaglandin $F1_\alpha$; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; NO = nitric oxide; $P(A\text{-}a)O_2$ = alveolar-arterial oxygen partial pressure difference; Qs/Qt = intrapulmonary shunt fraction; RIA = radioimmunoassay; SPV = selected pulmonary vasodilator; $\dot{V}/\dot{Q}$ = ventilation/perfusion ratio

Hypoxemia is by definition[1] present in varying degrees in all patients with ARDS. Occasionally the hypoxemia is severe enough to pose an increased risk of morbidity or mortality, either intrinsically or due to oxygen toxicity sustained during therapy. When this is the case, the use of a selective pulmonary vasodilator (SPV) may offer some therapeutic advantages by improving the ventilation/perfusion ratio ($\dot{V}/\dot{Q}$).

Theoretically, an SPV is delivered in the inspiratory gas only to areas of ventilated lung. The SPV, with a very short duration of action, then exerts its vasodilator effect on pulmonary vessels within the ventilated lung unit. This, in turn, improves blood flow to the ventilated regions, which is a heterogeneous/regional process in ARDS, and improves the

*From the Department of Pharmacology (Dr. van Heerden), University Department of Medicine (Dr. Barden), and Biostatistical Consulting Service (Mr. Bulsara), Department of Public Health, University of Western Australia, Nedlands, Australia; Department of Haematology (Mr. Michalopoulos), PathCentre, Perth, Australia; and Department of Intensive Care (Ms. Roberts), Sir Charles Gairdner Hospital, Perth, Australia.
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Correspondence to: P.V. van Heerden, MD, Department of Intensive Care, Sir Charles Gairdner Hospital, Hospital Avenue, Nedlands, WA 6009, Australia; e-mail: vernon@iinet.net.au

$\dot{V}/\dot{Q}$. The selectivity demonstrated by these agents is, therefore, twofold: first, with respect to the effect only on the pulmonary and not the systemic circulation; and, second, due to the effect only on vessels within ventilated lung units. Nitric oxide (NO) has been used extensively in this role since the 1980s.[2,3] More recently, inhaled aerosolized prostacyclin (IAP) delivered by jet or ultrasonic nebulizer also has been used as an SPV for hypoxemia in patients with ARDS.[4–13] Currently, there is sufficient evidence to support the role of IAP as an SPV for hypoxemia due to ARDS, in addition to its use in the treatment of pulmonary hypertension.[14–17] However, dose-response relationships for IAP vs indexes of oxygenation and systemic and pulmonary pressures have not been clearly defined.

The aims of this study were to determine the presence or absence of dose-response relationships of IAP (over the dose range 0 to 50 ng/kg/min) vs indexes of oxygenation (Pa_{O_2}/fraction of inspired oxygen [F_{IO_2}] ratio and alveolar-arterial oxygen partial pressure difference [$P(A\text{-}a)O_2$]), vs cardiovascular parameters (cardiac index [CI], mean arterial pressure (MAP), and mean pulmonary artery pressure [MPAP]), and vs shunt fraction. In addition, the systemic levels of one of the major metabolites of prostacyclin, 6-keto prostaglandin $F1_\alpha$ (6-ketoPGF1_α), were measured to determine the extent of systemic absorption of prostacyclin during IAP therapy. Due to the ephemeral nature of the parent compound, it is not possible to readily measure prostacyclin levels. Platelet function studies were carried out to detect any antiplatelet effect of the circulating systemic 6-ketoPGF1_α.

Materials and Methods

Patients

Institutional ethics committee approval was obtained prior to enrolling patients in this study. Nine adult patients, six men and three women with a mean age of 62 years (range, 33 to 77 years) and a mean acute physiology and chronic health evaluation (APACHE) II score [18] of 16 (range, 8 to 20), were enrolled in the study. Inclusion criteria were the following: witnessed informed consent; age $\geq$ 18 years; receiving mechanical ventilation in the ICU; and ARDS due to any cause. All patients had a lung injury score of $\geq$ 2.5 (mean, 2.7; range, 2.5 to 3), indicating severe ARDS by this scoring system.[19] Exclusion criteria were the following: a bleeding diathesis (international normalized ratio, $\geq$ 1.5; or activated partial thromboplastin time, $\geq$ 45 s); or any head injury. Patients were entered into the study on the day of their ICU stay on which the ARDS became severe, as defined by the lung injury score.[19] Patient diagnoses and demographic details are listed in Table 1.

The subjects were all inpatients in the Department of Intensive Care at the Sir Charles Gairdner Hospital, Perth, Western Australia. Patients received mechanical ventilation (Siemens Servo 900C mechanical ventilator; Siemens; Elema, Sweden) via endotracheal tube or tracheotomy tube during the study period. Sedative agents (titrated infusions of morphine and midazolam) and muscle relaxants as required (intermittent bolus doses of vecuronium titrated to effect) were administered to enable patient compliance with tracheal intubation and mechanical ventilation.

The F_{IO_2} (mean, 0.6; range, 0.5 to 1.0) (Table 1) was titrated to produce a Pa_{O_2} of at least 50 mm Hg. Minute ventilation (Table 1) was adjusted to maintain the Pa_{CO_2} within the physiologic range (35 to 45 mm Hg) where the pulmonary pathology permitted. Peak inflation pressure was maintained at $\leq$ 40 cm H_2O in all instances (allowing mean tidal volumes of approximately 8 mL/kg). Ventilator parameters were not altered during the study period.

Patients were maintained in the supine position, with a maximum "head-up" elevation of 15° throughout the study period (maximum time, 4 h). During this time, no nursing interventions (*eg*, washing, dressing changes, and airway suctioning), drug administration, or IV fluid bolus administration were permitted. Constant infusions of sedative agents, vasopressors, inotropes, and maintenance fluids present prior to study enrollment were continued unchanged during the study period.

Physiologic Monitoring

All subjects enrolled in the study had the following types of physiologic monitoring.

Pressures. Invasive arterial BP (systolic, diastolic, and mean pressures) was measured via a 20-gauge cannula situated in the radial artery and connected to a physiologic monitor (Sirecust 1261; Siemens Medical Systems, Inc; Iselin, NJ) via a fluid-filled

Table 1—*Patient Demographic, Diagnostic, and Ventilation Data

Patient No.	Age, yr	Sex	APACHE II Score	LIS	Diagnosis	ICU Day	$\dot{V}_E$, L/min	PEEP, cm H_2O	F_{IO_2}
1	51	M	14	3	Legionella pneumonia	2	12.4	10	0.8
2	75	M	19	3	AAA repair	13	21	12	0.75
3	56	M	20	2.5	Pancreatitis	3	12	10	0.5
4	77	M	8	2.5	Aspiration pneumonitis	2	22.4	10	0.5
5	76	M	11	2.75	Pancreatitis	13	11.2	2.5	0.6
6	52	F	20	2.75	Pneumococcal pneumonia	3	18	5	0.5
7	68	F	20	2.75	Pulmonary contusion	8	21	10	0.5
8	70	M	20	2.5	Gram-neg septicemia	6	9	10	0.55
9	33	F	16	2.5	Adrenal surgery	2	10.3	5	1.0

*LIS = Murray lung injury score; $\dot{V}_E$ = minute ventilation; PEEP = positive end-expiratory pressure; AAA = abdominal aortic aneurysm; M = male; F = female.

pressure transducing system (Abbott Critical Care Systems; Salt Lake City, UT). The following specific types of pressures were measured:

1. Mean central venous pressure was measured using the same monitor, connected to a 16-gauge central venous catheter that was placed in the superior vena cava via either the internal jugular or subclavian routes.
2. Pulmonary arterial pressures (systolic, diastolic, and mean pressures) were measured using the same monitor connected to the distal lumen of a 5-lumen, 7.5F, balloon-tipped, flow-directed pulmonary artery catheter (model AH-05050-H; Arrow International; Reading, PA) placed in either the left or right pulmonary artery via either the internal jugular or subclavian venous routes.
3. Pulmonary capillary wedge pressure was measured following inflation of the balloon of the catheter, described above, with not > 1.5 mL of air, with the trace then "frozen" on the monitor screen and the measurement made at the end of patient expiration. Pulmonary capillary wedge pressure was measured immediately before measuring cardiac output (CO) in each instance.

All pressures were zeroed with reference to the mid-axillary line.

CO. CO was measured using the standard thermodilution technique. Three 10-mL boluses of cold 5% dextrose water were injected into the subject's right atrium via the pulmonary artery catheter randomly during the respiratory cycle. The three measurements (provided that the values were within 10% of each other) were averaged and stored. The monitor automatically calculated the CI from the measured CO and from the patient's mass and height.

Pulse Oximetry. Continuous pulse oximetry was employed in all patients.

Blood Gas Measurements

Blood gas measurements were carried out every 30 min at each dose interval (seven measurements per patient) using blood drawn from both the radial arterial line ("arterial") and the right atrial port of the pulmonary artery catheter ("mixed venous"). For each measurement, 1 mL of blood was drawn into a blood gas syringe containing 50 U zinc heparin (Martell Medical Products, Inc; Morganton, NC) and was analyzed within 5 min on a blood gas analyzer (ABL 520; Radiometer Medical A/S; Bronshoj, Denmark). All results were measured or calculated at a corrected patient temperature of 37°C. Pao_2 and $P(A\text{-}a)O_2$ were calculated using the standard equations. The mixed venous blood sample results (not tabulated) were used to calculate the intrapulmonary shunt fraction (Qs/Qt) by the standard equation

$$Qs/Qt = CcO_2 - CaO_2/CcO_2 - C\bar{v}O_2,$$

where C is content, a is arterial, $\bar{v}$ is mixed venous, and c is pulmonary capillary, as described in the study by Zwissler et al.[20]

Drug Delivery

Prostacyclin Aerosol. The synthetic analog of prostacyclin, epoprostenol sodium (Flolan; Glaxo Wellcome; Boronia, Victoria, Australia) is supplied in vials of 500 μg. This is diluted in a 0.188% w/v solution of glycine in saline solution (0.147% w/v) prior to administration, which we term the "diluent." The diluent is highly alkaline, with a pH range of 10.2 to 10.8, and is more viscous than normal saline solution.

IAP was delivered continuously by jet nebulizer (Sidestream jet nebulizer; Medic-Aid Ltd; West Sussex, UK) into the inspired gas being delivered to the subject, as depicted in Figure 1. The mass median diameter of diluted prostacyclin particles produced by this jet nebulizer was 3.38 μm, as measured by laser particle analyzer (model MS20; Malvern Instruments Ltd; Malvern, UK). The nebulizer (C in Fig 1) was constantly replenished with prostacylin solution that was delivered by a syringe pump (A in Fig 1). The FIO_2 of the nebulizer driving gas (E in Fig 1) was the same as that being delivered by the mechanical ventilator. The FIO_2 of gas being delivered to the patient by the mechanical ventilator was not, therefore, altered by the addition of the driving gas to the ventilator circuit. The nebulizer driving gas was delivered at a pressure of 420 cm H_2O via a flowmeter at 6 L/min. However, the mechanical ventilator compensated for the additional gas flow into the ventilator circuit, so that positive end-expiratory pressure and the mean and peak airway pressures were unaltered. The exhaled minute ventilation registered by the pneumotachograph of the ventilator, however, included the increased gas flow provided by the driving gas.

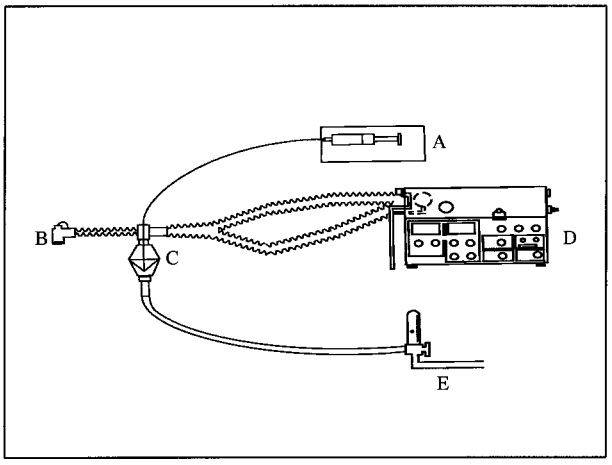

FIGURE 1. IAP delivery system. A = syringe pump delivering epoprostenol solution; B = patient end of ventilator tubing; C = jet nebulizer; D = mechanical ventilator; E = nebulizer driving the gas at 6 L/min.

The jet nebulizer was placed as close as possible to the catheter mount connection (B in Fig 1) to minimize the loss of aerosol in the exhaled gas or as "rain-out" in the ventilator circuit tubing. Rain-out was further minimized by heating and humidifying all inspired gas (model 328 water bath humidifier; Fisher and Paykel Healthcare Ltd; Auckland, New Zealand). The humidifier was set at a temperature of 40°C.

The actual mass of IAP deposited in the respiratory tract by this technique is not known, as some of the nebulized particles are lost by rain-out in the ventilator circuit and some are exhaled. That sufficient drug is deposited in the distal respiratory tree is inferred from the observed clinical effect and from the optimal respirable size of the particles produced by the jet nebulizer.

The concentration of prostacyclin solution to be delivered at each dose increment was determined by adding appropriate volumes of the diluent to the vial of epoprostenol/prostacyclin. In this way, six syringes were produced of equal volume with 0, 10, 20, 30, 40, or 50 μg/mL concentrations of prostacyclin solution. The delivered dose of IAP could then accurately be increased every 30 min, in increments of 10 ng/kg/min, over the dose range 0 to 50 ng/kg/min. This was accomplished by using the syringe with the appropriate concentration solution, at the required rate (*eg*, to deliver 50 ng/kg/min to a 70-kg subject, the syringe containing 50 μg/mL would be loaded in the syringe pump and

run at 4.2 mL/h into the nebulizing bowl of the jet nebulizer). The nebulizer was primed with 1 mL of the new concentration at the start of each 30-min period/increment change.

The aim of the 30-min dosing interval was to reach a steady physiologic state at each dose of IAP. This relatively short interval would, however, also limit confounding physiologic changes as a result of the underlying disease process. Once the maximum dose of 50 ng/kg/min had been delivered for 30 min, the dose was reduced again to 0 ng/kg/min for a further 30 min to determine whether physiologic parameters returned to baseline values.

Measurement of 6-KetoPGF1$_\alpha$ Levels

Prostacyclin is an ephemeral substance with a biological half-life of 2 to 3 min. It is rapidly hydrolyzed to its major metabolite 6-ketoPGF1$_\alpha$ *in vitro* and *in vivo*.[21–25] 6-ketoPGF1$_\alpha$ is more stable in circulation than the parent compound, and its level is measurable in plasma.[22] Plasma levels of 6-ketoPGF1$_\alpha$ were measured as an estimate of the degree of absorption of the parent compound from the respiratory tract into the pulmonary system and, thence, into systemic circulation. Any 6-ketoPGF1$_\alpha$ detected in the serum necessarily would be contributed to by the hydrolysis of both endogenous prostacyclin and exogenous (administered) prostacylin.

Blood for the measurement of plasma 6-ketoPGF1$_\alpha$ levels was drawn from the arterial line. Seven milliliters of blood was drawn using a plastic syringe and was then immediately injected slowly into a 10-mL blood collection tube via a 19-gauge needle. These siliconized glass tubes had previously been prepared by adding 500 IU sodium heparin (volume, 0.5 mL), to prevent coagulation, and 36 μg acetylsalicylic acid, to inhibit cyclooxygenase activity (and therefore the continued production of endogenous prostacyclin) in the glass tube. These samples were placed in a centrifuge within 5 min of collection and were spun at 4,000 rotations per minute for 10 min. The plasma then was decanted by pipette into plastic storage tubes, which were stored at −70°C until analysis.

Analysis of plasma levels of 6-kPGF1$_\alpha$ was by radioimmuoassay (RIA). ^{3}H 6-ketoPGF1$_\alpha$ (5,000 counts per minute) was added to plasma (1 mL) for the estimation of recovery. The sample was extracted with two volumes of acetone. After centrifugation at 2,000*g* for 10 min, the neutral lipids were extracted into two volumes of hexane. The sample was centrifuged again, the hexane layer was removed, and the pH of the sample was adjusted to 4. The sample then was extracted with two volumes of chloroform, was centrifuged at 2,000*g* for 10 min, and the aqueous phase was discarded. The organic phase containing 6-ketoPGF1$_\alpha$ was taken to dryness in a centrifugal evaporator and was reconstituted in methanol.

The 6-ketoPGF1$_\alpha$ sample was separated from other prostanoids using thin-layer chromatography and a solvent system containing chloroform/methanol/acetic acid/water (135:75:24:150). The 6-ketoPGF1$_\alpha$ band was identified by running a standard containing ^{3}H 6-ketoPGF1$_\alpha$. The bands corresponding to 6-ketoPGF1$_\alpha$ were scraped, and the 6-ketoPGF1$_\alpha$ was extracted into 0.1 mol/L phosphate-buffered saline solution at pH 7.5 (1 mL). The sample was centrifuged, and the supernatant was divided for estimation of recovery and quantitation of 6-ketoPGF1$_\alpha$ by RIA.

The RIA utilized an ^{125}I histamine 6-ketoPGF1$_\alpha$ label antibody and standards ranging from 0 to 200 pg/mL. The bound 6-ketoPGF1$_\alpha$ was separated by the addition of dextran-coated charcoal, and the bound fraction was counted in a γ counter. The recovery of ^{3}H 6-ketoPGF1$_\alpha$ through the procedure was about 45%, and the within- and between-assay variations were 5% and 12%, respectively.

Platelet Aggregation Studies

Blood samples were obtained from the radial arterial line into a vacuum tube blood collection system (Vacutainer; Becton Dickinson; Franklin Lakes, NJ). Each sample was collected into a siliconized glass tube containing one part 3.8% sodium citrate per nine parts blood. Platelet aggregation studies were carried out on these samples within 10 min after collection if possible, or the samples were batched and the studies were performed within 2 h of collection while the samples were gently agitated on an agitation table.

The samples were centrifuged at 150*g* for 15 min to produce platelet-rich plasma and at 1,500*g* for 20 min to obtain platelet-poor plasma. The platelet-rich plasma was diluted with platelet-poor plasma to a final platelet count of approximately 250×10^9/L. Platelet aggregation was performed using an aggregation recorder (Daiichi Monitor IV; Helena Laboratories; Beaumont, TX). Platelet aggregation was induced with adenosine diphosphate sodium salt in a buffer (Sigma Chemical Co; St Louis, MO) in a final concentration of 1 μmol/L. The extent of aggregation, both the maximal extent and that achieved after 4 min, was determined.

Statistical Analysis

A generalized linear regression model

$$Yij = \mu + Si + \alpha j + Eij$$

where $i = 1,2 \ldots 9$ patients, $j = 1,2 \ldots 7$ doses, *Yij* is the outcome for patient *i* under dose *j*, *Si* is the random subject effect, αj is the dose effect, and *Eij* is the random error, was used to determine the presence of a positive or negative gradient on each measured or calculated variable over the dose range of the IAP employed in the study (0 to 50 ng/kg/min). A p value ≤ 0.05 was used to define a significant increase or decrease in each variable in response to an increasing dose of IAP, which was independent of chance and factors related to repeated measures in the same subjects.

Statistical Power

According to the method of Wong and Lachenbruch,[26] a sample size of five subjects would be adequate at the 90% power level ($1 - \beta$) to show a dose-response relationship for shunt fraction, three subjects for P(A-a)O_2, two subjects for PaO_2/FIO_2 ratio, and two subjects for prostacyclin metabolite levels. The power calculation was performed for seven doses at a level of significance (α) of 0.05, based on a two-tailed test. The method of power calculation is described in detail by Wong and Lachenbruch.[26] A minimal sample size of 62 subjects would have been required to show a dose-response effect on platelet function, at the 90% power level, due to the wide variability of platelet function results, as discussed below.

In addition, the Wilcoxon rank sum test for related measures was used to compare PaO_2/FIO_2 ratio, P(A-a)O_2, and Qs/Qt at IAP doses of 0, 10, and 50 ng/kg/min. The Wilcoxon rank sum test also was used to compare the parameters at baseline (dose, 0 ng/kg/min) and at the end of the study (dose, 0 ng/kg/min).

Statistical analysis was carried out using the computer software (SAS/STAT Software, version 6.12; SAS Institute; Cary, NC)

Results

The results are depicted in Figure 2 and in Tables 2 and 3. All values shown graphically are mean values (n = 9), error bars in Figure 2 indicate the SEM.

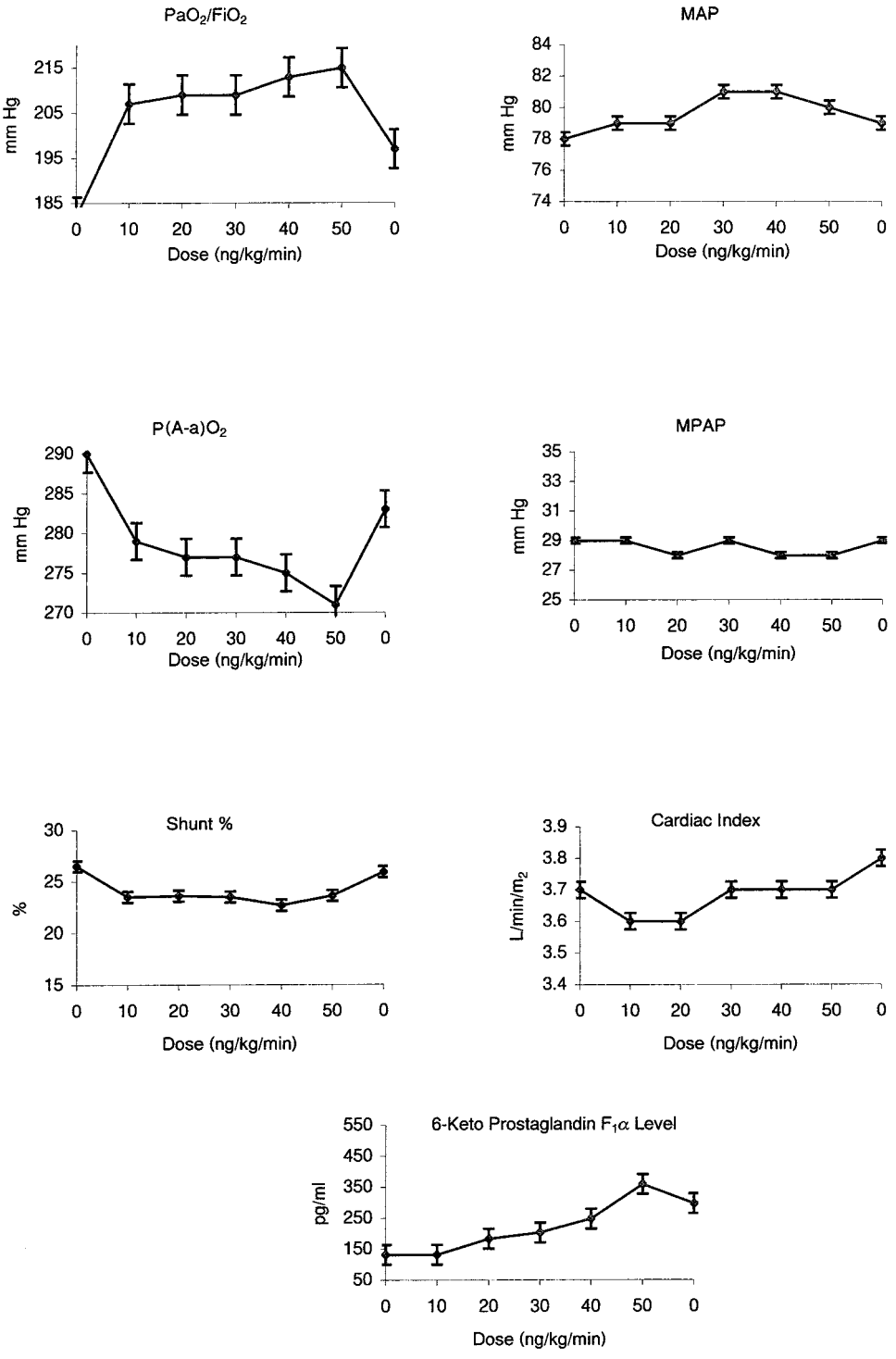

FIGURE 2. The dose-related effects of IAP. Values are given as the mean (n = 9).

Indexes of Oxygenation

The PaO_2/FIO_2 ratio showed a significant ($p = 0.003$) dose-dependent increase (parameter estimate, 5.3) by generalized linear regression model. The $P(A\text{-}a)O_2$ gradient also decreased over the study period (parameter estimate, −3.0; $p = 0.01$). The largest incremental improvement (*ie*, difference in mean values between successive dose intervals) in both values was between the baseline (IAP dose, 0 ng/kg/min) and 10 ng/kg/min. The graphs in Figure 2 illustrate this and the subsequent reduction in rate of dose-related change in each parameter (flattening of the slope).

The maximum effect (largest change from base-

line, as determined by the difference between the mean values at baseline and the subsequent dose) was produced by the maximum dose of IAP (50 ng/kg/min). The reduction in Qs/Qt with increasing IAP dose tended toward statistical significance ($p = 0.07$), with a slightly negative gradient (parameter estimate, −0.49).

The indexes of oxygenation both returned to baseline when the 50 ng/kg/min dose was discontinued. There was no significant statistical difference between the Pao_2/Fio_2 ratio ($p = 0.1$) and $P(A\text{-}a)O_2$ ($p = 0.4$) at the start of the study period (IAP dose, 0 ng/kg/min) vs the end of the study period (IAP dose, 0 ng/kg/min).

Comparison using the Wilcoxon test for related measures at IAP doses of 0, 10, and 50 ng/kg/min for Pao_2/Fio_2, $P(A\text{-}a)O_2$, and shunt fraction are shown in Table 2. The results indicate no statistical differences in the parameters between IAP doses of 10 and 50 ng/kg/min or between IAP doses of 0 and 10 ng/kg/min, despite the largest incremental change occurring for this step from 0 to 10 ng/kg/min (see above). The p values for the Pao_2/Fio_2 ratio and the Qs/Qt (0 vs 10 ng/kg/min) approach significance. There is a statistical difference for the Pao_2/Fio_2 ratio between IAP doses of 0 and 50 ng/kg/min, while the p values for $P(A\text{-}a)O_2$ and Qs/Qt approach significance (Table 2). However, the values tabulated in Table 2 were no longer statistically significant when the Bonferroni correction for multiple comparisons was applied. The p value for significance in this instance then became < 0.003.

Table 3 shows the individual values of the Pao_2/Fio_2 ratio for the nine patients at each dose interval.

Cardiovascular Parameters

There was no statistically significant dose-related change in MPAP ($p = 0.38$), although there was a trend toward increase in MAP ($p = 0.07$) and CI ($p = 0.06$) over the course of the study period. None of the patients entered into the study had significant pulmonary hypertension (mean MPAP, 29 mm Hg; range, 24 to 43 mm Hg).

6-ketoPGF1$_\alpha$ Plasma Level

There was a linear and significant ($p = 0.001$) increase in plasma levels of this prostacyclin metabolite over the study period (parameter estimate, 41.6). The maximum level of 6-ketoPGF1$_\alpha$ was seen at the maximum dose of IAP, as determined by the difference in the mean values of 6-ketoPGF1$_\alpha$ at a dose of 0 ng/kg/min vs a dose of 50 ng/kg/min of IAP. The level of 6-ketoPGF1$_\alpha$ trended toward baseline when the dose of 50 ng/kg/min was discontinued (Fig 2).

Platelet Function Studies

There was no demonstrable effect of a dose of IAP vs platelet function as determined either by maximum aggregation or aggregation at 4 min. In the case of both parameters, there was a wide variation between subjects at baseline and at each subsequent dose interval. The mean values (and range) for the two measurements at baseline were the following: maximum aggregation, 41% (range, 15 to 100%); and aggregation at 4 min, 35% (range, 5 to 100%). The parameter estimates were 1.203 for maximum aggregation (SEM, 0.896; $p = 0.186$) and 0.863 for aggregation at 4 min (SEM, 0.916; $p = 0.351$) in response to the increasing dose of IAP, as determined by the generalized linear regression model.

Discussion

This study demonstrates the basic properties of IAP as an SPV. This potent vasodilator, when inhaled, results in an improvement in oxygenation, without a systemic hypotensive effect in this group of patients with severe ARDS. What this study also shows is that this effect is dose-responsive, at least over the dose range used in the study.

The blunting of the initial rapid improvement in oxygenation (incremental change, 0 to 10 ng/kg/min) may be due to recirculation of the 6-ketoPGF1$_\alpha$, which then acts as a nonselective pulmonary vasodilator as it reenters the pulmonary circulation. This

Table 2—*Comparison of the Median Values of Pao_2/Fio_2 Ratio, $P(A\text{-}a)O_2$, and Qs/Qt at IAP Doses 0, 10, and 50 ng/kg/min

Indexes	IAP Dose, ng/kg/min		
	0 vs 10	0 vs 50	10 vs 50
Pao_2/Fio_2 ratio, mm Hg	187.2 vs 183.2	*187.2 vs 202.2*	183.2 vs 202.2
$P(A\text{-}a)O_2$, mm Hg	238 vs 247	238 vs 237	247 vs 237
Qs/Qt, %	28 vs 21.4	28 vs 18	21.4 vs 18

*$p < 0.008$ approaches significance, allowing for the Bonferroni correction for multiple comparisons.

Table 3—*Individual Pa_{O_2}/F_{IO_2} Ratio Values for Each Patient**

Patient No.	IAP Dose, ng/kg/min						
	0	10	20	30	40	50	0
Pa_{O_2}/F_{IO_2}							
1	105.5	97.4	108.5	116.1	126.6	137.2	135.5
2	97.1	182.4	110.9	98.9	102.8	100.8	86.8
3	212	231.4	201	231.6	231	262.8	255.2
4	155.2	150.8	155	165.4	160	171.6	166.4
5	129.2	146.5	155.3	146.2	155.5	145	109.3
6	358.4	420.4	416	410.2	398.6	367.2	367.6
7	187.2	183.2	193.6	198.8	205.6	202.2	179.4
8	189	212.7	280	251	291	284	225
9	204	235	257	260	245	267	244
Mean	181.9	206.6	208.6	208.7	212.9	215.3	196.6

*Values given are for Pa_{O_2}/F_{IO_2} ratio in mm Hg for each dose.

assumption, however, is not supported by a marked reduction in MPAP as 6-ketoPGF1$_\alpha$ levels increase or by the fact that the maximum improvement in oxygenation is seen at the highest dose of IAP (*ie*, an ongoing improvement in oxygenation as the dose increases).

Indeed, there was no marked effect on MPAP, and this is probably because of the relatively normal baseline value in the study group. The fact that the CI did not significantly change also serves to demonstrate the efficacy of IAP as an SPV. The total blood flow through the lung was unchanged, but because oxygenation improved it is assumed that the flow is redirected within the lung from nonventilated to ventilated areas, thus improving $\dot{V}/\dot{Q}$ matching. This is borne out by a reduction in Qs/Qt with increasing doses of IAP. That IAP achieves its effect in the manner described above is supported by the efficiency of the drug delivery system (shown in Fig 1), which is able to generate respirable particles of prostacyclin in glycine buffer solution. These respirable particles are delivered to ventilated areas of the lung.

The study also demonstrated a significant dose-responsive increase in systemic serum levels of prostacylin metabolite. A systemic hypotensive effect due to 6-ketoPGF1$_\alpha$, a less potent vasodilator than the parent compound, was not seen in this group of patients. Platelet dysfunction due to systemic absorption of prostacyclin and its metabolites also was not demonstrated by this study. This is in conflict with both previous *in vivo* [27] and *in vitro* [28] studies, in which extremely low levels of prostacyclin and its metabolites have been shown to produce potent antiplatelet effects.

The inability of this study to demonstrate dose-responsive antiplatelet effects may relate to the wide variation in baseline values in this group of very ill patients, indicating disordered platelet function on entry into the study. The effects due to systemically absorbed prostacyclin/6-ketoPGF1$_\alpha$ may not, therefore, be apparent due to the high level of background "noise." This noise would not be present in controlled *in vitro* studies [28] or *in vivo* studies in volunteers.[27] In any event, an antiplatelet effect within the pulmonary circulation has theoretical advantages in patients with ARDS, where platelet and white cell aggregation are part of the pathologic process.[29–32]

In patients with ARDS, SPV therapy is primarily directed at the severe hypoxemia associated with the syndrome. In this role, an SPV may be able to improve oxygenation, allowing a reduction in F_{IO_2} during mechanical ventilation to less toxic levels. Oxygen toxicity remains a real concern when treating ARDS.[33] Second, SPV therapy also may be utilized to treat the pulmonary hypertension seen occasionally in patients with ARDS or pulmonary hypertension from other causes. This study does not address that issue.

The only similar study of which the authors are aware that addresses the dose-response relationship between IAP and oxygenation and hemodynamic indexes is by Zwissler et al.[20] That study investigated the dose-response relationships of 0, 1, 10, and 25 ng/kg/min of IAP vs oxygenation and hemodynamic indexes, in which the dose was increased every 15 min. The study was able to demonstrate an effect, though modest, on MPAP, that our study was not able to demonstrate. That study also did not investigate 6-ketoPGF1$_\alpha$ levels or the possible effect those levels might have on platelet function. The two studies concur on a number of points: there is a significant dose-related effect of IAP on oxygenation in patients with ARDS (using similar statistical methods); there is no significant difference between various doses of IAP on indexes of oxygenation when effects at different doses are compared (Table 2); the best improvement in oxygenation occurred between

0 and 10 ng/kg/min; and there was no significant effect on Qs/Qt in either study. Both studies also demonstrate the individual variations in response to the same dose range of IAP with respect to extent and timing of response. IAP, like NO therapy, and indeed as for other vasoactive therapies, requires titration to individual responses. In this way, the lowest but most effective dose is chosen for maximum effect with minimum adverse effects. The current study would support 10 ng/kg/min as a reasonable starting dose of IAP for hypoxemic patients with ARDS.

Inhaled prostacyclin and NO have now both been well demonstrated to fulfill the role of an efficacious SPV. IAP has the advantage of simplicity of delivery, being a viable SPV in the operating room and in the emergency transport environment. Currently, a number of other agents are undergoing investigation as SPVs, including other eicosanoids,[34] NO donors,[35] and zaprinast.[36] Their major roles remain the treatment of hypoxemia and pulmonary hypertension. The additional administration of an enhancer of hypoxic pulmonary vasoconstriction such as almitrine bimesylate may improve the $\dot{V}/\dot{Q}$ matching effect of the SPV, which is another area that requires further study.

Conclusion

This study confirms the efficacy of IAP as an SPV for the treatment of hypoxemia due to ARDS. The study also demonstrates the dose-related actions of IAP when delivered by this simple delivery system.

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P. Vernon van Heerden, Anne Barden, Nicholas Michalopoulos, Max K. Bulsara and Brigit L. Roberts

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