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Functional and Metabolic Activity of Polymorphonuclear Leukocytes from Patients with Adult Respiratory Distress Syndrome: Results of a Randomized Double-Blind Placebo-Controlled Study on the Activity of Prostaglandin E_1

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Indirect and experimental evidence suggests that polymorphonuclear leukocytes, responding to an activating signal presumably related to the complement cascade activation, are involved in the pathogenesis of the adult respiratory distress syndrome (ARDS). The pathologic changes seem to be result of the polymorphonuclear leukocyte margination within the pulmonary capillary vessels and their activation with subsequent release of vasoactive peptides (thromboxane A_2, prostaglandin E_2) and toxic intracellular compounds. This study confirms that adherence, chemotaxis, and chemiluminescence are increased in polymorphonuclear leukocytes from patients with ARDS. Enhanced chemotactic and chemiluminescence capacities are likely specific to ARDS, whereas increased polymorphonuclear leukocyte adherence seems to be nonspecific. If increased polymorphonuclear leukocyte activation is important in the pathogenesis of ARDS, the inhibition of this phenomenon could play a therapeutic role. This double-blind prospective study was undertaken to assess if polymorphonuclear leukocyte activity is inhibited *in vivo* by the iv administration of prostaglandin E_1 (PGE_1) in patients with ARDS. A continuous infusion of PGE_1 at a dose of 30 $ng \cdot kg^{-1} \cdot min^{-1}$ for 7 days did not modify the functional activity of polymorphonuclear leukocytes in patients with ARDS. Because hemodynamic instability was seen during infusion of this dose of PGE_1, an increased dose was not tested. At the dose of PGE_1 tested, no significant effect upon the function activity of polymorphonuclear leukocytes in patients with ARDS could be demonstrated. (Key words: Lung: adult respiratory distress syndrome. Polymorphonuclear leukocytes. Prostaglandin E_1.)

CHAOTIC COMPLEMENT ACTIVATION resulting in polymorphonuclear leukocyte activation and sequestration in pulmonary capillary vessels appears to play a central role in the pathogenesis of the adult respiratory distress syndrome (ARDS).[1] Polymorphonuclear leukocyte margination within the lungs and their adherence to the endothelial cells result in an increased oxygen consumption together with the hexose monophosphate shunt activation.[2] The subsequent production of reactive oxygen-free radicals, neutral proteases, and lysosomal enzyme increases lung microvascular permeability.[1] In addition to these products, polymorphonuclear leukocytes have the capacity to produce other biologic components of the inflammatory response, such as cyclooxygenase and lipooxygenase metabolites, consistent with the increase in lung permeability and pulmonary pressure.[3] As reported by Zimmerman *et al.*,[4] the state of activation of polymorphonuclear leukocytes appears to be significantly higher in patients with ARDS than in patients without ARDS.

Prostaglandin E1 (PGE_1) has been shown to have several actions that are of potential benefit in the treatment of ARDS. PGE_1 inhibits oxygen-free radical release by polymorphonuclear leukocytes pretreated with a chemotactic agent.[5] PGE_1 inhibits polymorphonuclear leukocyte adherence to endothelial cells, by suppressing the release of leukotriene B4,[6] and prevents increased lung microvascular permeability.[7] PGE_1 may act on polymorphonuclear leukocytes either through an increase in intracellular cyclic adenosine monophosphate (AMP) levels or by antagonizing the aggregatory effects of thromboxane.[8,9]

PGE_1 is also a potent vasodilator of both systemic and pulmonary circulations.[10,11] In patients with ARDS, PGE_1 reduces mean arterial and mean pulmonary arterial pressures, and increases arterial oxygen content by increasing cardiac index.[12,13] Because PGE_1 is almost completely metabolized on a single passage through the lung[14] and has a short half-life (30 s), its use appears safe in critically ill patients because any adverse effect disappears after dose reduction or discontinuation of the infusion.[15]

The current study studied the functional polymorphonuclear leukocyte state of activation in patients with ARDS and determined prospectively if a continuous iv infusion of PGE_1 could modify the metabolic activation state of polymorphonuclear leukocytes sampled either from patients with ARDS or from patients without ARDS.

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Materials and Methods

Patients

Twenty-three surgical critically ill (n = 14) or multiple trauma patients (n = 9), admitted to the Surgical Intensive Care Unit of la Pitié Hospital (Paris) from September 1985 to October 1987, were included in a prospective randomized, placebo-controlled double-blind study. In each case informed consent was obtained from the closest relatives. The clinical protocol was approved by the Human Investigation and Ethic Committee of the hospital. The inclusion criteria were as follows: 1) presence of hypoxemia requiring an inspired oxygen fraction (F_{IO_2}) of 0.5 or greater to achieve a Pa_{O_2} greater than 60 mmHg, and 2) radiographic evidence of diffuse pulmonary infiltrates without evidence of left ventricular failure (pulmonary capillary wedge pressure < 12 mmHg) or previous chronic obstructive pulmonary disease.

At the time of inclusion, all patients were receiving parenteral antibiotics, 12 were receiving iv catecholamines (dopamine, dobutamine, and/or epinephrine), 16 morphine, 17 flunitrazepam. None were receiving corticosteroids or anti-inflammatory drugs. Patients were randomly assigned to receive either a continuous iv infusion of PGE_1 or a continuous iv infusion of placebo. Eleven patients (nine men and two women) were included in the PGE_1 group and 12 patients (seven men and five women) were included in the placebo group. The clinical characteristics of the patients are summarized in table 1.

The patients received a continuous 7-day iv infusion of either PGE_1 in an ethanol base (Prostin VR_{TM}, Alprostatil) or placebo (ethanol base only). The infusion was given through a central venous catheter and administered in incremental doses of 5, 10, 15, 20, and 25 $ng \cdot kg^{-1} \cdot min^{-1}$ at 30-min intervals and then at a constant rate of 30 $ng \cdot kg^{-1} \cdot min^{-1}$ for 7 days. Hemodynamic parameters were measured prior to the administration of PGE_1 or placebo and 15 min after each step. Measurements were repeated at least twice a day during the infusion period.

TABLE 1. Clinical Characteristics of the Patients Studied at the Time of Inclusion in the Study (mean ± SD)

	PGE_1 Group (n = 11)	Placebo Group (n = 12)
Age (yr)	45 ± 13	42 ± 17
Duration of mechanical ventilation (days)	24 ± 23	20 ± 18
Static respiratory compliance* (ml/cmH_2O)	58 ± 13	54 ± 17
Survivors	7	4
PaO_2 at FIO_2 1 (mmHg)	123 ± 51	118 ± 54
MPAP (mmHg)	19 ± 5	21 ± 8
PCWP (mmHg)	8 ± 3	10 ± 5
CI ($l \cdot min^{-1} \cdot m^{-2}$)	4.11 ± 0.99	4.86 ± 1.17

MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; CI = cardiac index.

* Static respiratory compliance was measured using a 2-l syringe through step-by-step inflation–deflation (50 ml at each step).

There were no significant differences between the PGE_1 group and the placebo group.

Polymorphonuclear leukocyte functional status was evaluated within a mean of 28 h (range, 7–46 h) from the time ARDS criteria were satisfied. Evaluation of polymorphonuclear leukocyte functional activity including chemotaxis, chemiluminescence, and adherence was performed within the 4 h preceding the beginning of the iv infusion (control) and repeated during the first, third, fifth, and seventh day of infusion. A final evaluation was performed 7 days after the end of the infusion. Polymorphonuclear leukocyte functional activity was also measured in ten critically ill patients without any clinical or radiologic evidence of ARDS (Pa_{O_2} at F_{IO_2} 1 during intermittent positive pressure = 365 ± 52 mmHg). These patients were all suffering from severe neuromuscular disease and their lungs were mechanically ventilated for extrapulmonary reasons. All were receiving antibiotics, but none were treated by catecholamines or anti-inflammatory drugs. In addition, reference values for adherence, chemotactic, and chemiluminescence responses of normal polymorphonuclear leukocytes were obtained from 11 healthy volunteers.

Assays for Polymorphonuclear Leukocyte Activities

Sample collections. In patients with ARDS, 30 ml blood samples were withdrawn simultaneously from a peripheral artery and from the pulmonary artery, at control, day 1, 3, 5, 7, and 14. In patients without ARDS and in healthy volunteers, a single blood sample was withdrawn either from a peripheral artery or from a peripheral vein.

Polymorphonuclear leukocyte preparation. Heparinized blood was immediately transported to the laboratory, mixed with an equal volume of 24:10 mixture of Dextran T-500 (9% solution in normal saline) and Radioselectan® (38% solution in normal saline) and allowed to stand for 1 h at room temperature. The polymorphonuclear leukocyte-enriched band of cells above the erythrocyte pellet was collected and washed twice with phosphate-buffered saline by centrifugation (1,500 rpm). The purity and the viability of the polymorphonuclear leukocytes were more than 90%, as checked using standard staining methods.

Polymorphonuclear leukocyte chemiluminescence. Polymorphonuclear leukocyte chemiluminescence was evaluated as follows[16]: purified polymorphonuclear leukocytes resuspended in 20 ml of Hank's balanced solution were adjusted to 5 × 10 cells per ml before 30 μl of luminol solution was added. The cell suspension was assayed for

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chemiluminescence using a Picolite-luminometer Analyzer®, which detects the number of emitted photons per minute and adapted for 10 min to the dark. All assays were performed at 37° C. Chemiluminescence background was monitored and polymorphonuclear leukocyte activation was then performed by adding 100 μl of opsonized zymosan. Following zymosan injection the chemiluminescence was monitored for 20 min by means of a chart recorder. The chemiluminescence peak was reached after 5 ± 2 min after zymosan injection. A duplicate assay was performed for each sample. The polymorphonuclear leukocyte activity was expressed as maximum chemiluminescence of the cells minus basal chemiluminescence because the integration of the chemiluminescence curve did not provide better results than the measurement of the chemiluminescence peak.

Polymorphonuclear leukocyte chemotaxis. Polymorphonuclear leukocyte chemotaxis in agarose was studied using the method described by Nelson *et al.*[17] Agarose was dissolved in sterile distilled Kreb's solution by heating in a boiling water bath for 25–30 min. After cooling to 46° C, the agarose solution was mixed with heat-inactivated fetal calf serum (9% vol/vol final concentration). Five milliliters of the agarose solution was delivered to 60 × 15 mm Petri dishes. The dishes were then transferred to the refrigerator for 30–60 min. Eight series of three wells of 2.4 mm diameter and spaced 2.5 mm apart were cut in each Petri dish using a template and stainless steel punch. Leukocytes (10/ml) were resuspended in phosphate-buffered saline and 5 μl was deposited in the center well. The outer well received 5 μl of nonchemotactic control medium (phosphate-buffered saline). Plasma collected from venous blood from type AB rhesus-positive healthy volunteers, from the blood bank of the Salpêtrière Hospital, was treated with Zymosan as a source of activated C5 fragments. This plasma contained an activity stable at 56° C and aggregated granulocytes in a dose-dependent fashion. This activity remains stable in plasma prepared using this method for at least 10 months when frozen at −70° C. Dishes were incubated at 37° C in a 5% CO_2 atmosphere. Dishes were examined microscopically using a ×40 objective squared (5 × 5 mm) ocular lens. The distance of migration was always determined by the same observer and was calculated by measurements of the linear distance the cells have moved from the margin of the well toward the chemotactic factor. A chemotactic index of polymorphonuclear leukocyte migration (defined as specific directed motility minus nonspecific motility = A − B) was measured in eight replicates for each blood sample assayed and expressed in millimeters.

Polymorphonuclear leukocyte adherence. Polymorphonuclear leukocyte adherence to nylon fiber columns was measured according to the technique described by Thong and Currell.[18] Adherence to nylon fiber columns was used because experimental evidence has been published demonstrating a strong correlation between adherence to nylon fibers and adherence to endothelial cells.[19] Briefly, a nylon fiber column of 10 mg is inserted into a micropipette plastic tip: 10 cells/ml are delivered in duplicate in these columns and are incubated for 30 min at 37° C. After vacuum was immediately determined using a coulter counter, adherence was calculated in percentage of adherent polymorphonuclear leukocytes (total polymorphonuclear leukocytes assayed minus nonadherent collected polymorphonuclear leukocytes) divided by the total number of polymorphonuclear leukocytes assayed.

Statistical Analysis

All data were expressed as mean + SD. Comparisons of polymorphonuclear leukocyte functions over time within groups were performed using a one-way analysis of variance (ANOVA), followed by a modified Student's *t* test for paired data. Because the number of patients decreased with time, an ANOVA for repeated measures design was also performed for each subgroup of patients. Comparison of polymorphonuclear leukocyte functions in control healthy volunteers, and in patients with and without ARDS were performed by a modified Student's *t* test for unpaired data. $P < 0.05$ was considered statistically significant.

Results

Functional Activation of Polymorphonuclear Leukocytes in Patients with ARDS

All patients with ARDS exhibited an increased polymorphonuclear leukocyte count. The absolute number of polymorphonuclear leukocytes was not different in the pulmonary arterial blood and in the systemic arterial blood (13,728 ± 6,022 *vs.* 13,903 ± 5,163 polymorphonuclear leukocytes/ml).

Chemiluminescence. As shown in table 2, the polymorphonuclear leukocyte peak chemiluminescence was significantly higher in patients with ARDS compared with patients without ARDS or healthy volunteers. When expressed as a percentage of healthy volunteer values, the peak chemiluminescence generated by polymorphonuclear leukocytes from patients with ARDS was 176 ± 22%.

Polymorphonuclear leukocyte migration. The polymorphonuclear leukocyte chemotactic index was significantly higher in patients with ARDS than in patients without ARDS or in healthy volunteers. When expressed as a percentage of healthy volunteer values, the chemotactic index of polymorphonuclear leukocytes from patients with ARDS was 219 ± 17%.

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TABLE 2. Evaluation of Polymorphonuclear Leukocyte Functional Activity in Critically Ill Patients with and Without ARDS and in Healthy Volunteers

	Healthy Volunteers (n = 11)	Critically Ill Patients Without ARDS (n = 10)	Patients with ARDS (n = 23)
Chemotactic index (mm)	1.13 ± 0.68	1.43 ± 1.13	A 2.47 ± 0.95* AP 2.02 ± 1.23*
Chemiluminescence (beats/min × 10^7)	1.10 ± 0.23	1.07 ± 0.61	A 2.00 ± 0.98* AP 1.95 ± 0.04*
Adherence	66 ± 6	80 ± 7†	A 83 ± 10† AP 80 ± 12†

A = systemic arterial blood samples; AP = pulmonary arterial blood samples.
* $P < 0.01$ *versus* healthy volunteers and critically ill patients without ARDS.
† $P < 0.05$ *versus* healthy volunteers.

Adherence. Polymorphonuclear leukocyte adherence was significantly higher in critically ill patients with and without ARDS than in healthy volunteers. When expressed as percentage of healthy volunteer values, polymorphonuclear leukocyte adherence was 121 ± 3.7% in patients with ARDS and 121 ± 4% in patients without ARDS. Polymorphonuclear leukocyte adherence, chemotaxis, and chemiluminescence were similar in pulmonary arterial and systemic arterial blood samples.

EFFECT OF PGE_1 IN PATIENTS WITH ARDS

In the PGE_1 group four patients died (36%) 12 h, 5 days, and 6 days after inclusion in the study. Histologic analysis of lung biopsies evidenced bacterial pneumonia (n = 3) and nonspecific diffused alveolar damage (n = 1). In the placebo group seven patients died (58%) within a mean time of 4 days (range, 1–19 days) after inclusion in the study. In five patients histologic analysis of lung biopsies evidenced bacterial pneumonia (n = 2), massive pulmonary contusion (n = 2), and nonspecific diffuse alveolar damage (n = 1). The difference observed in the mortality rate of each group did not reach statistical significance. As shown in table 3, iv infusion of PGE_1 in patients with ARDS did not significantly modify polymorphonuclear leukocyte functional activity. Within each group chemotaxis, chemiluminescence, and adherence did not significantly change throughout the study.

A major problem associated with PGE_1 administration was its hypotensive effect. PGE_1 had to be suddenly interrupted in two patients because of arterial hypotension resistant to catecholamine administration. Among the nine remaining patients who tolerated PGE_1 infusion, four were already receiving catecholamines before their inclusion in the study. In three patients catecholamine infusion rate had to be increased to maintain an acceptable level of systolic arterial pressure after 1 h of 30 $ng \cdot kg^{-1} \cdot min^{-1}$ PGE_1 infusion. In three other patients catecholamines had to be added to avoid systolic hypotension. In another patient significant hypotension occurred at day 2, requiring a decrease in the PGE_1 infusion rate from 30 to 20 $ng \cdot kg^{-1} \cdot min^{-1}$. In the placebo group no significant hemodynamic changes were noted after the iv infusion.

Discussion

Because PGE_1 has anti-inflammatory properties that could be potentially beneficial in patients with ARDS,[6,20] this double-blind study was conceived to evaluate whether PGE_1 could attenuate the functional activation of polymorphonuclear leukocytes in patients with ARDS, reduce lung injury, and improve mortality rate. Unfortunately, these hypotheses could not be confirmed. PGE_1 infused iv at a dose of 30 $ng \cdot kg^{-1} \cdot min^{-1}$ during 7 days did not decrease the adherence, chemiluminescence, and chemotaxis of polymorphonuclear leukocytes obtained from

TABLE 3. Comparative Evaluation of Polymorphonuclear Leukocyte Functional Activity in Patients with ARDS Receiving Either iv PGE_1 or Placebo for 7 Days

	N	Control	N	Day 1	N	Day 3	N	Day 5	N	Day 7	N	Day 14
Chemotaxis (mm)												
PGE_1	11	2.96 ± 0.75	9	2.08 ± 0.97	7	2.83 ± 1.16	6	3.52 ± 0.62	5	3.49 ± 1.10	4	3.35 ± 1.61
Placebo	12	2.02 ± 1.23	11	2.31 ± 1.13	10	2.25 ± 1.03	4	2.85 ± 1.48	4	2.99 ± 1.41	4	3.54 ± 1.07
Chemiluminescence (beats/min × 10^7)												
PGE_1	10	2.11 ± 0.88	8	1.75 ± 1.92	7	1.83 ± 0.97	6	1.57 ± 0.72	5	1.55 ± 0.50	4	1.55 ± 0.49
Placebo	12	1.91 ± 1.14	11	2.02 ± 1.45	10	1.63 ± 0.97	4	1.74 ± 1.36	4	1.96 ± 0.75	4	1.39 ± 0.81
Leukocyte adherence (%)												
PGE_1	11	87 ± 10	10	85 ± 7	7	82 ± 8	6	82 ± 5	5	81 ± 10	4	81 ± 6
Placebo	12	80 ± 11	10	84 ± 8	10	82 ± 10	3	88 ± 3	3	85 ± 3	3	84 ± 3

Because PGE_1 infusion had to be stopped in two patients (for severe leucopenia and marked arterial hypotension) and because of several patient's death, the number of patients in whom polymorphonuclear leukocyte functional activity could be evaluated decreased with time. N = number of patients in whom polymorphonuclear leukocyte functional activity could be evaluated.

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11 patients with severe acute respiratory failure. This result does not confirm *in vitro* studies in which PGE_1 was shown to suppress polymorphonuclear leukocyte activation.[9,21] Because PGE_1 activity is clearly dose-dependant, one reason for this discrepancy could be that an insufficient dose was administered to the patients. However, the recommended dose in clinical practice (30 $ng \cdot kg^{-1} \cdot min^{-1}$) cannot be exceeded without significant adverse hemodynamic changes.[12,13] In awake healthy humans a dose of 100 $ng \cdot kg^{-1} \cdot min^{-1}$ decreased mean arterial pressure by 8.6%,[22] whereas in patients with ARDS, as demonstrated by this study, a dose of 30 $ng \cdot kg^{-1} \cdot min^{-1}$ decreased mean arterial pressure by 20% or more. Therefore, even if larger doses of PGE_1 might have inhibited polymorphonuclear leukocyte activation, it would be unwise to recommend these higher doses in patients with ARDS in whom hemodynamic instability is frequently observed. This difference in PGE_1 hemodynamic effects could be explained by a significant decrease in PGE_1 lung extraction in patients with ARDS[23] leading to higher plasma concentration of PGE_1.[14] Another hypothesis to explain why PGE_1 was ineffective in reducing polymorphonuclear leukocyte activation in patients with ARDS is the existence of a polymorphonuclear leukocytes mediated pulmonary injury not inhibited by prostaglandin action. It is well known that neutrophils produce oxygen-free radicals in two ways: one being inhibited by PGE_1, the other being independent of prostaglandin inhibition.[5]

Our results also confirm a previous study demonstrating that polymorphonuclear leukocytes obtained from pulmonary and peripheral blood samples collected at the early phase of ARDS are functionally activated.[4] We found that chemotactic and chemiluminescence capacities of polymorphonuclear leukocytes from patients with severe ARDS were significantly greater than those of critically ill patients without ARDS. In contrast to the study by Zimmerman *et al.*,[24] increased polymorphonuclear leukocyte adherence was found in all critically ill patients studied with and without ARDS, suggesting that leukocyte adherence is likely not specific to acute lung damage. The increased polymorphonuclear leukocyte chemiluminescence is generally related to the production by polymorphonuclear leukocytes of different reactive oxygen species, including superoxide anions, hydrogen peroxide, hydroxyl radicals, and singlet molecular oxygen,[16] which can directly injure the alveolar-capillary membrane.[1] Therefore, augmented chemiluminescence is highly suggestive of a potential role for polymorphonuclear leukocytes in the genesis of ARDS.

Chemotaxis under agarose is a simple and reproducible method for measuring chemotaxis and spontaneous migration of polymorphonuclear leukocytes.[17] Increased polymorphonuclear leukocyte chemotaxis found in patients with ARDS suggests the existence of chemoattractants within the circulation. The existence of many chemotactic factors, such as complement factors and macrophage-derived factors, have been evidenced in patients with ARDS.[25] It has been previously demonstrated that the adherence of human polymorphonuclear leukocytes to nylon fiber and human endothelial cells is similar.[19] Because it is generally assumed that the adherence of polymorphonuclear leukocytes to vascular endothelium constitutes the first step of polymorphonuclear leukocyte aggregation within the lungs in ARDS,[1] the increased adherence found in the group of patients with ARDS could be interpreted as indirect proof of their role in the genesis of ARDS. However, this is not likely because we also found increased polymorphonuclear leukocyte adherence in critically ill patients without ARDS. Moreover, in a previous study normal polymorphonuclear leukocyte adherence was reported in critically ill patients with ARDS.[24] These conflicting results are likely related to the fact that many factors, in addition to lung disease, can influence polymorphonuclear leukocyte adherence, such as circulating catecholamines,[26] platelet count,[27] C5 a fragment,[28] and sepsis.[29] Finally, because 18 patients in this study were septic and some of them were receiving iv catecholamines, it is not surprising to have found increased polymorphonuclear leukocyte adherence.

In summary, these results confirm that polymorphonuclear leukocytes from patients with ARDS have a greater capacity of migration and free radical oxygen production, which seems specific to lung injury, whereas polymorphonuclear leukocyte adherence is much more influenced by extrapulmonary factors. PGE_1, 30 $ng \cdot kg^{-1} \cdot min^{-1}$ was not found to be effective in reducing polymorphonuclear leukocyte activation in patients with ARDS. Because arterial hypotension was frequently associated with PGE_1 administration, higher doses were not tested and should not be recommended in patients with ARDS and hemodynamic instability.

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