Possible Prognostic Value of Leukotriene B_4 in Acute Respiratory Distress Syndrome

Joan R Masclans MD PhD, Joan Sabater MD, Judit Sacanell MD, Pilar Chacon MD PhD, Pilar Sabin MD PhD, Oriol Roca MD, and Mercè Planas MD PhD

OBJECTIVE: To study the major eicosanoids implicated in the pathophysiology of acute respiratory distress syndrome (ARDS) in order to estimate their relative prognostic values. METHODS: We conducted a prospective study in a consecutive series of patients with ARDS admitted to a university hospital intensive care unit. We measured the plasma concentrations of 3 inflammatory mediators (thromboxane B_2, 6-keto prostaglandin $F_{1\alpha}$, and leukotriene B_4) in peripheral arterial and mixed venous plasma samples. RESULTS: We studied 16 patients with ARDS, who had a mean ± SD baseline ratio of P_{aO_2} to fraction of inspired oxygen (P_{aO_2}/F_{IO_2}) of 147 ± 37 mm Hg and a mean ± SD baseline lung injury score of 2.9 ± 0.37. The plasma concentrations of thromboxane B_2, 6-keto prostaglandin $F_{1\alpha}$, and leukotriene B_4 were greater than the general-population reference levels in both arterial and mixed venous plasma, but only leukotriene B_4 was higher in arterial plasma than in mixed venous plasma (401 ± 297 pg/mL vs 316 ± 206 pg/mL, $p = 0.04$). When we correlated the eicosanoid concentrations with specific indicators of clinical severity, we found correlations only between the baseline P_{aO_2}/F_{IO_2} and the arterial thromboxane B_2 level ($r = -0.57$, $p = 0.02$), the arterial leukotriene B_4 level ($r = -0.59$, $p = 0.01$), and the transpulmonary gradient of leukotriene B_4 level ($r = -0.59$, $p = 0.01$). We also found a correlation between the transpulmonary gradient of leukotriene B_4 and the lung injury score ($r = 0.51$, $p = 0.04$). The thromboxane B_2 concentration in arterial plasma and the leukotriene B_4 concentration in both arterial and mixed venous plasma were the only baseline plasma eicosanoid concentrations that predicted significant differences in outcome. When looking at the transpulmonary gradient of the eicosanoids studied, we found that only the gradient of leukotriene B_4 showed significant differences of clinical interest. Among survivors we observed practically no gradient (−4.9%), whereas among nonsurvivors we found a substantial positive gradient of 41.6% for the elevated arterial (post-pulmonary) values, compared with the pulmonary-artery (pre-pulmonary) values, and this difference was statistically significant ($p = 0.02$). CONCLUSIONS: The pro-inflammatory eicosanoid leukotriene B_4 showed the best correlation with lung-injury severity and outcome in patients with ARDS. *Key words: acute respiratory distress syndrome, ARDS, leukotriene B_4, thromboxane B_2, prostacyclin, prognostic value, outcome.* [Respir Care 2007;52(12):1695–1700. © 2007 Daedalus Enterprises]

Introduction

Acute respiratory distress syndrome (ARDS) is characterized by severe acute respiratory insufficiency, and each year it may affect as many as 200,000 people in the United States alone. Despite recent advances in mechanical ventilation, ARDS is associated with great (co)morbidity and

Joan R Masclans MD PhD, Joan Sabater MD, Judit Sacanell MD, and Oriol Roca MD are affiliated with the Intensive Care Unit; Pilar Chacon MD PhD is affiliated with the Department of Biochemistry; Pilar Sabin MD PhD is affiliated with the Department of Pharmacy; and Mercè Planas MD PhD is affiliated with the Nutritional Support Unit, Hospital Universitari Vall d'Hebron, Barcelona, Spain.

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greater than 40% mortality.[1–3] A large number of factors have been implicated in the development of ARDS. Examples include various vasoactive substances and agents that promote cell aggregation and modify permeability, such as histamine, serotonin, the cytokine system, and some lipid mediators (prostaglandins, leukotrienes, and platelet-activating factor). The use of biological markers to establish prognostic indicators in ARDS should improve outcome prediction and optimize therapeutic decisions.[4]

Arachidonic acid is a polyunsaturated essential fatty acid that is converted to various biologically active derivatives, including lipid mediators, also known as eicosanoids.[5] The cyclooxygenase enzyme adds 2 oxygen molecules to form endoperoxide G_2, the common precursors of eicosanoids, known as prostanoids. These constitute a chemical family of cyclic compounds (prostaglandins and thromboxanes). If one molecule of oxygen is added, the lipoxygenase enzyme facilitates the synthesis of other metabolically active eicosanoids called leukotrienes.

The lungs are a major site of eicosanoid synthesis. Prostaglandin I_2 (also known as prostacyclin) and thromboxane A_2 are considered the most important arachidonic acid derivatives in the lungs. Thromboxane A_2 increases pulmonary vascular resistance, whereas prostacyclin dilates the pulmonary vascular bed. Leukotriene B_4 is the major arachidonic acid derivative produced via 5-lipoxygenase, and it is released by alveolar macrophages and neutrophils. Unlike with other compounds produced via similar metabolic pathways (leukotrienes C_4, D_4, and E_4), which are potent bronchoconstrictors, the main effect of leukotriene B_4 is related to the inflammatory response, and it facilitates capillary extravasation.[6] Antonelli et al suggested that leukotrienes may play an important role in the pathophysiological chain of events that starts with a cellular lesion and may constitute a key factor in the development of ARDS.[7]

The pulmonary hypertension observed in ARDS could be due to the action of various vasoconstrictor lipid mediators (thromboxane A_2 in particular) and to blockade of vasodilator prostanoids, with an apparent role as modulators of pulmonary hypertension (prostaglandin I_2 in particular). These conclusions are based on observations in animals and humans. Blockade or modulation of these arachidonic acid derivatives might have a role in the management of ARDS. Clinical studies have looked at the effects of blockade of the formation of vasoconstrictor prostaglandins at various points in the inflammatory pathway—mostly aiming to block phospholipase A and cyclooxygenase—and at the effects of stimulating an increase in the concentrations of vasodilator prostaglandins. However, clinical efficacy results were inconclusive.[8,9] Our study group has worked on this topic before, studying the possible modulation of eicosanoids as a function of fatty acid intake in parenteral nutrition,[10] as well as the potential hemodynamic effects such fat emulsions may have in the presence of an imbalance between those mediators.[11] Although the prognostic values of baseline eicosanoid concentrations for outcome prediction in ARDS previously observed by us are weak, there is clearly a tendency for such correlations.[12]

The objective of the present study was to determine the plasma concentrations of major arachidonic acid derivatives potentially involved in the pathophysiology of ARDS, and to estimate the prognostic value of these mediators for outcome prediction in ARDS.

Methods

Patients

We conducted a prospective study in a consecutive series of 16 patients with ARDS admitted to the ICU of the Hospital Universitari Vall d'Hebron, Barcelona, Spain, within the first 48 hours that they met the diagnostic criteria of ARDS of the American-European Consensus Conference on ARDS.[1] The study was approved by the appropriate ethics committee.

Outcome Measures

The following variables were recorded/calculated: baseline ratio of P_{aO_2} to fraction of inspired oxygen (P_{aO_2}/F_{IO_2}) at the time the patient met the ARDS diagnostic criteria, lung injury score,[13] Acute Physiology and Chronic Health Evaluation (APACHE II) score,[14] number of days on mechanical ventilation, duration of ICU stay, and survival.

Eicosanoid Assays

We determined thromboxane B_2, a stable metabolite of the potent vasoconstrictor thromboxane A_2, and 6-keto prostaglandin $F_{1\alpha}$, a stable metabolite of the vasodilator prostacyclin, as typical arachidonic acid derivatives of the cyclooxygenase pathway, and leukotriene B_4, a potent proinflammatory compound, as an arachidonic acid derivative of the lipoxygenase pathway.

These eicosanoids were determined in arterial plasma (post-pulmonary) and in mixed venous plasma (pre-pulmonary) by electroimmunoassay (Amersham International, Buckinghamshire, United Kingdom). We used EDTA (ethylenediaminetetraacetic acid) as an anticoagulant, to avoid "in-plasma" activation of leukocytes by indomethacin.

Correspondence: Joan R Masclans MD PhD, Servei de Medicina Intensiva, Area General, Hospital Universitari Vall d'Hebron de Barcelona, Passeig Vall d'Hebron, 119–129, 08035 Barcelona Spain. E-mail: jrmasclans@vhebron.net.

For each study eicosanoid we calculated the arterial/mixed-venous (transpulmonary) gradient to provide a noninvasive measure of any specific intrapulmonary behavior of these compounds. This gradient was calculated by subtracting the eicosanoid concentration in mixed venous plasma from that in arterial plasma.

The arterial plasma samples were drawn from a peripheral arterial catheter while the mixed venous plasma samples were obtained from a Swan-Ganz catheter.

The reference ranges used were those determined in healthy individuals by the same laboratory in our institution.

Statistical Analysis

The data were imported from a database (Access, Microsoft, Redmond, Washington) to statistics software (SPSS, SPSS, Chicago, Illinois). The following statistical variables were calculated for numerical variables: mean, standard deviation, and range (where appropriate). Differences between the means were analyzed via the Mann-Whitney U test for independent samples and the Wilcoxon signed rank test for related samples. Correlations were analyzed via Spearman's correlation coefficient. The level of statistical significance was defined as $p < 0.05$.

Results

Of the 16 patients studied, 14 were men (87.5%). Their mean age was 55 ± 16 y. At the time of meeting the diagnostic criteria for ARDS, the patients had a mean ± SD P_{aO_2}/F_{IO_2} of 147 ± 37 mm Hg, a mean ± SD lung injury score of 2.9 ± 0.37, and a mean ± SD APACHE II score of 14 ± 3. Seventy-five percent of the patients had ARDS of intrapulmonary origin, due to severe community-acquired pneumonia in 7 cases (44%) and bronchoaspiration in 4 cases (25%). The remaining 5 ARDS cases were due to smoke inhalation, status post-pneumectomy, pancreatitis, mediastinitis, or extrapulmonary sepsis. Patients were treated with a lung-protective ventilation strategy.

Table 1. Plasma Eicosanoid Concentrations

	Plasma Eicosanoid Concentration (mean ± SD pg/mL)		
	Thromoxane B_2	Leukotriene B_4	6-Keto-Prostaglandin $F_{1\alpha}$
Reference (normal) value	< 150	< 75	< 50
Baseline arterial	284 ± 127	401 ± 297	523 ± 208
Baseline mixed venous	329 ± 139	316 ± 206	584 ± 237
p for baseline arterial versus mixed venous plasma	0.06	0.04	0.36
p for arterial mixed venous versus reference values	0.02	0.01	0.001

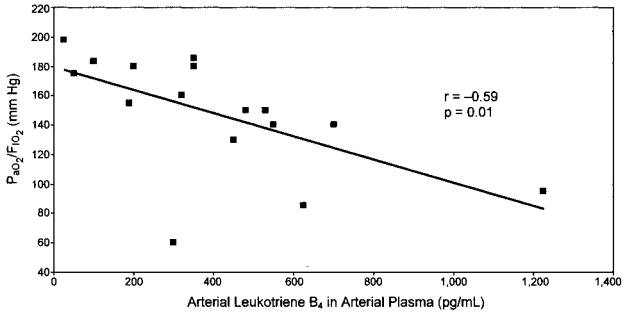

Fig. 1. Correlation between baseline ratio of P_{aO_2} to fraction of inspired oxygen (P_{aO_2}/F_{IO_2}) and baseline leukotriene B_4 concentration in arterial plasma.

The mean ± SD days on mechanical ventilation was 21 ± 19 d, and the mean ± SD duration of ICU stay was 29 ± 23 d. Seven patients (43.8%) died, mainly from multiple-organ failure.

Table 1 shows the baseline plasma concentrations of thromboxane B_2, leukotriene B_4, and 6-keto prostaglandin $F_{1\alpha}$. All the eicosanoid concentrations in these patients with ARDS, in both the arterial and the mixed venous plasma samples, were higher than the general-population reference levels. Analysis of the differences between prepulmonary and post-pulmonary plasma concentrations of the individual eicosanoids revealed, however, that leukotriene B_4 was the only eicosanoid to show substantial differences in this regard: the leukotriene B_4 concentration in the arterial plasma was significantly higher than that in pulmonary artery (mixed venous) plasma (401 ± 297 pg/mL vs 316 ± 206 pg/mL, $p = 0.04$).

When we correlated the eicosanoid concentrations with specific indicators of clinical severity (both mixed venous and arterial), we found correlations only between the baseline P_{aO_2}/F_{IO_2} and arterial thromboxane B_2 concentration ($r = -0.57$, $p = 0.02$), arterial leukotriene B_4 concentration ($r = -0.59$, $p = 0.01$) (Fig. 1), and the transpulmonary gradient of leukotriene B_4 ($r = -0.59$, $p = 0.01$). We also found a correlation between the transpulmonary gradient of leukotriene B_4 and the lung injury score ($r = 0.51$, $p = 0.04$).

Figures 2, 3, and 4 show the mean baseline concentrations of the 3 study eicosanoids as a function of outcome for both types of plasma sample. The thromboxane B_2 concentration in arterial plasma and the leukotriene B_4 concentration in both arterial and mixed venous plasma were the only baseline plasma eicosanoids to predict significant differences in outcome.

When looking at the transpulmonary gradient of the eicosanoids studied, we found that only the transpulmonary gradient of leukotriene B_4 showed significant differ-

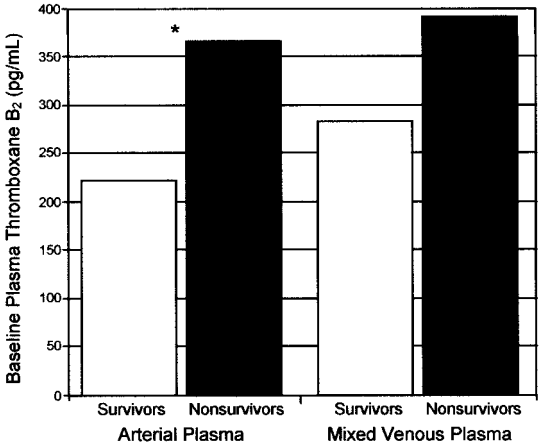

Fig. 2. Baseline plasma thromboxane B_2 concentrations in arterial and mixed venous plasma as a function of survival. * For arterial plasma concentration, $p = 0.03$. For mixed venous plasma concentration, $p = 0.14$.

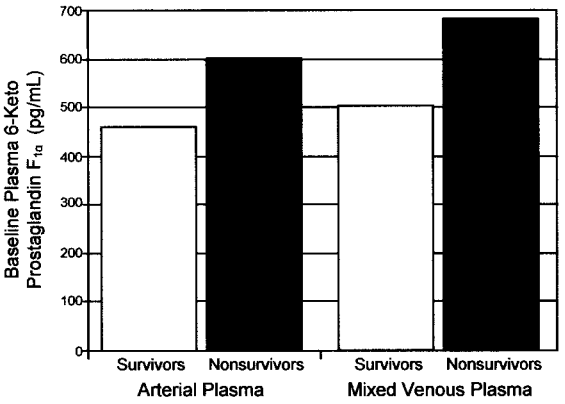

Fig. 3. Baseline plasma 6-keto prostaglandin $F_{1\alpha}$ concentrations in arterial and mixed venous plasma as a function of survival. For arterial plasma concentration, $p = 0.25$. For mixed venous plasma concentration, $p = 0.35$.

ences of clinical interest (Fig. 5). Among survivors we observed practically no gradient (−4.9%), whereas among nonsurvivors we found a substantial positive gradient (41.6%) for the elevated arterial values compared with the mixed venous values, and this difference was statistically significant at $p = 0.02$.

Discussion

We studied a series of relatively young patients (mean age 55 y) with severe acute lung injury, as demonstrated by a mean lung injury score of 2.9 ± 0.37 and a baseline P_{aO_2}/F_{IO_2} of 147 ± 37 mm Hg, whereas mortality was similar to that of series with a better prognosis.

Our results show that, though the plasma concentrations of all study eicosanoids were higher than those in healthy

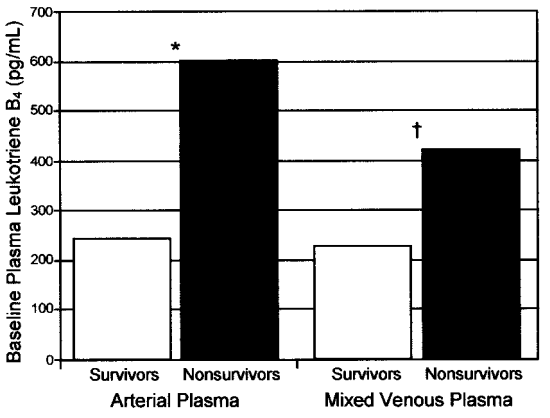

Fig. 4. Baseline plasma leukotriene B_4 concentrations in arterial and mixed venous plasma as a function of survival. * For arterial plasma concentration, $p = 0.01$. † For mixed venous plasma concentration, $p = 0.04$.

controls, only the plasma levels of thromboxane B_2 and leukotriene B_4 were correlated with lung injury severity, and may have predictive value for outcome in patients with ARDS.

Apart from their basic gas-exchange function, the lungs are also a site where metabolic processes take place. In fact, the lungs are involved in both the synthesis and breakdown of various inflammatory mediators, such as the phospholipid derivatives commonly known as eicosanoids.[15] The arachidonic acid derivatives (eicosanoids) of the cyclooxygenase pathway include thromboxanes and prostaglandins (prostacyclin), whereas leukotrienes are arachidonic acid derivatives of the lipoxygenase pathway. Platelet-activating factor is another compound that is derived from membrane phospholipids and might also have a role in the pathophysiology of inflammation, but its metabolism uses a different enzymatic pathway.[16,17]

ARDS is associated with a wide variety of pulmonary and nonpulmonary risk factors that may impact the development and outcome of the syndrome. Factors produced in the arachidonic acid cascade are involved in the pathophysiology of ARDS. Whereas thromboxane and prostacyclin have traditionally been thought to have key roles in lung-injury formation, recent evidence suggests that arachidonic acid derivatives of the lipoxygenase pathway may have a more central role here.

Early evidence that implicated eicosanoids in the pathophysiology of ARDS came from studies in which the cyclooxygenase pathway was blocked. Although there have been isolated reports that cyclooxygenase blockade is associated with a potential improvement in pulmonary gas exchange, no study could definitively establish the clinical efficacy of this approach.[18,19] It has also been postulated that corticosteroid use in patients with ARDS, with the aim of blocking the inflammatory cascade by blocking the phospholipase enzyme, might improve outcomes in patients

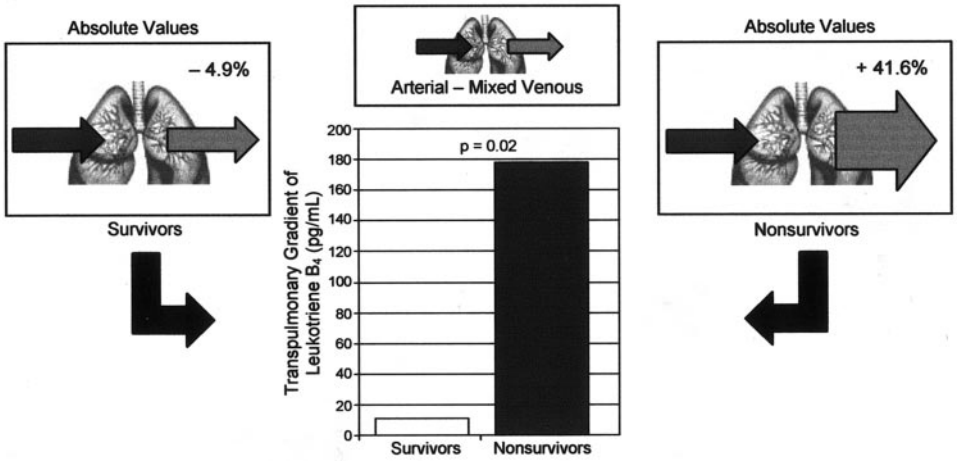

Fig. 5. Transpulmonary gradient of leukotriene B_4 levels (arterial minus mixed venous plasma concentration) as a function of survival.

with ARDS, but this intervention also produced negative results.[20] Using a different tack, a number of authors tried stimulating an increase in the plasma concentrations of vasodilator prostaglandins, but the clinical utility of this approach could not be demonstrated.[21–23]

However, leukotrienes in general, and leukotriene B_4 in particular, play a major role in leukocyte chemotaxis in the lungs, which in turn might trigger the remainder of the inflammatory cascade.[24] In fact, elevated leukotriene concentrations have been found in both the bronchoalveolar lavage fluid and the plasma of patients with lung injuries, as well as those at risk of developing lung injury.[25–27] In a recent paper, Caironi et al reported a central role of lipoxygenase pathway derivatives in the development of acute lung injury.[26]

Unlike other studies that looked only at one particular eicosanoid, we determined the pre-pulmonary and post-pulmonary concentrations of the major biologically active arachidonic acid derivatives produced along both major enzymatic pathways (cyclooxygenase and lipoxygenase). We could dispense with bronchoalveolar lavage (which frequently causes alterations, albeit usually transient ones) because we determined not only absolute plasma eicosanoid concentrations but also the transpulmonary gradient of eicosanoid levels, which is an indicator of potential prognostic value.

Our results show that, though the plasma concentrations of all study eicosanoids were above normal, significant differences between arterial and pulmonary-artery plasma levels were found only for leukotriene B_4.

When we correlated eicosanoid concentrations with specific indicators of ARDS severity, we found correlations between the degree of hypoxia (as measured by the baseline P_{aO_2}/F_{IO_2}) and arterial thromboxane B_2 concentration, arterial leukotriene B_4 concentration, and the transpulmonary gradient of leukotriene B_4 levels. We also found a correlation between the transpulmonary gradient of leukotriene B_4 and the lung injury score. In other words, greater arterial thromboxane B_2 and/or leukotriene B_4 levels are associated with a lower P_{aO_2}/F_{IO_2} (ie, greater hypoxemia), and a greater transpulmonary gradient is associated with greater ARDS severity.

With regard to outcome prediction, we found greater mortality among patients with greater baseline arterial thromboxane B_2 and leukotriene B_4 concentrations, greater baseline leukotriene B_4 concentrations in mixed venous plasma, and a greater transpulmonary gradient of leukotriene B_4 levels.

Given the limitations of our small but homogeneous series of patients, we can thus conclude from our observations that prostacyclin probably has a very minor role, compared with other eicosanoids. Thromboxane B_2 would appear to play an intermediate role, whereas leukotriene B_4 probably is a pro-inflammatory substance that has a fundamental role in the inflammatory cascade implicated in the development and outcome of ARDS. Moreover, as emerges from Figure 5, the observed differences between pre-pulmonary and post-pulmonary (transpulmonary gradient) leukotriene B_4 concentrations suggest that the amount of leukotriene B_4 in the lungs at the time the diagnosis of ARDS is established is a marker of poor outcome.

Conclusions

In this study we found evidence that supports the predictive utility of the transpulmonary gradient of these arachidonic acid derivatives, compared with measurements obtained from bronchoalveolar washings, which, in clinical practice, may be difficult to obtain because of the patient's critical condition. However, the exhaled-breath condensate method may be another interesting noninvasive technique in this difficult clinical situation.[27,28]

It is interesting to note that more than 75% of our patients presented with an intrapulmonary lung injury as the ARDS cause. It is difficult to extrapolate these results to another population. Because this is an exploratory study, the specific knowledge of the clinical utility of leukotriene B_4 measurements could require a prospective study for validation. In this way, research into the possible modulation of the lipoxygenase pathway may also be a promising future approach to further improving the outcome of patients with ARDS.

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