Combined nitric oxide inhalation, prone positioning and almitrine infusion improve oxygenation in severe ARDS

Thierry Gillart MD,
Jean E. Bazin MD,
Bernard Cosserant MD,
Dominique Guelon MD,
Louis Aigouy MD,
Odile Mansoor MD,
Pierre Schoeffler MD

Purpose: To determine the efficacy and side effects of prone positioning (PP) and nitric oxide (NO) inhalation, alone, associated, or combined with iv almitrine for the treatment of hypoxaemia in severe acute respiratory distress syndrome (ARDS).

Methods: Over a period of 20 months, 27 consecutive critically ill patients with severe ARDS (Murray score > 2.5 , $\text{PaO}_2/\text{FiO}_2 < 170$ after alveolar recruitment) were prospectively and randomly included. They inhaled NO for two hours at concentrations of 5 and 10 ppm for one hour each (H0-H2). One hour later, they were returned to the prone position for four hours (H3-H7). During the last two hours in this position (H5-H7), they were assigned to further inhalation of 10 ppm NO (Group B, $n = 9$) or to no further inhalation (Group A, $n = 9$). In group C ($n = 9$), the procedure for group B was combined with perfusion of $16 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ almitrine throughout the study.

Results: Compared with control values, two hours NO inhalation improves $\text{PaO}_2/\text{FiO}_2$ and shunt effect by $+28\%$ and -9% , PP by $+88\%$ and -27% , PP + almitrine by $+132\%$ and -28% , NO + almitrine by $+153$ and -28% , PP + NO by $+94\%$ and -29% , NO + PP + almitrine by $+327$ and -48% . NO inhalation reduces pulmonary vascular resistance. Other haemodynamic parameters remain unchanged, whatever the treatment. NO inhalation improves $\text{PaO}_2/\text{FiO}_2$ by over 20% in 50% of the patients and PP is effective in 78% of the cases.

Conclusion: Prone Position improves $\text{PaO}_2/\text{FiO}_2$ significantly more than NO alone but less than PP+ almitrine or NO+ almitrine. The best results are obtained with the association of NO + Prone position + Almitrine.

Objectif : Apprécier et comparer l'intérêt du décubitus ventral (DV), de l'inhalation de NO et de l'administration continue d'almitrine, seuls ou en association, dans le traitement de l'hypoxémie au cours du syndrome de détresse respiratoire aiguë (SDRA).

Méthode : Sur une période de 20 mois, 27 patients hospitalisés en réanimation avec un SDRA grave (score de Murray $> 2,5$, $\text{PaO}_2/\text{FiO}_2 < 170$ après recrutement alvéolaire) ont été inclus prospectivement et de manière randomisée. Ils ont bénéficié de l'inhalation de NO pendant 2 heures à la posologie de 5ppm pendant une heure puis 10ppm (H0-H2). Après une heure d'arrêt, on les a retournés 4 heures en décubitus ventral (H3-H7). De H5 à H7 un groupe A ($n = 9$) était traité par DV seul tandis que l'on ajoutait dans un groupe B ($n = 9$) l'inhalation de NO à 10 ppm. Un troisième groupe C ($n = 9$) bénéficiait d'une perfusion continue d'almitrine ($16 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) associée à cette même séquence thérapeutique.

Résultats : Par rapport à H0, 2 heures de NO améliorent le rapport $\text{PaO}_2/\text{FiO}_2$ et diminuent le shunt de $+28\%$ et -9% , le DV de $+88\%$ et -27% , les associations DV + almitrine de $+132\%$ et -28% , NO + almitrine de $+153$ et -28% , DV + NO de $+94\%$ et -29% , NO + PP + almitrine de $+327$ et -48% . L'inhalation de NO diminue les résistances vasculaires pulmonaires. Les autres paramètres hémodynamiques restent inchangés quel que soit le traitement institué. L'inhalation de NO améliore le rapport $\text{PaO}_2/\text{FiO}_2$ de plus de 20% chez 50% des patients tandis qu'avec le même critère d'efficacité, 78% des malades sont répondeur au DV.

Conclusion : Le DV s'avère plus efficace que le NO seul pour ce qui est d'améliorer le rapport $\text{PaO}_2/\text{FiO}_2$, mais moins que les associations DV + almitrine ou NO + almitrine. Les meilleurs résultats sont obtenus avec la trithérapie DV + NO + almitrine.

From the Department of Anaesthesia, University Hospital, Hôpital Gabriel Montpied, 30, Place Henri-Dunant, 63003 Clermont-Ferrand cedex, France; Phone: 33-04-7362-5706; Fax: 33-04-7362-5696.

Address correspondence to: Thierry Gillart MD.

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FIRST described by Ashbaugh *et al.* 30 yr ago,¹ acute respiratory distress syndrome (ARDS) has frequently been the subject of physiological, therapeutic and even nosological discussion.² It is a major problem in critical care units, with a high morbidity rate varying from 40 to 70%.^{3,4} Recent research has addressed new methods of ventilation such as inverse ratio mechanical ventilation, high frequency ventilation, permissive hypercapnia, extracorporeal membrane gas exchange, use of perfluorocarbon, and controlled pressure ventilation. In addition, pharmacological treatment, chiefly inhalation of nitric oxide (NO) which, since first used for ARDS in 1993 by Rossaint *et al.*,⁵ seems to have a very promising future.⁶⁻⁹ At the same time, improved physiopathological understanding has made it possible to draw optimum benefit from older techniques such as positive end expiratory pressure (PEEP) or prone positioning which, unfortunately, has not been accepted as a routine form of treatment, presumably due to problems encountered in nursing. None of the therapeutic innovations designed to enhance gas exchange has proved able, by itself, to improve survival. However, there is an improvement in mortality rates which should be attributed to better overall management and treatment combinations, the advantages of which need to be evaluated.

The aim of this study was to compare the efficacy and side effects of NO inhalation and prone positioning, in patients with ARDS. We attempted to evaluate the advantages of therapeutic combinations, by the concomitant addition of continuous almitrine perfusion within the framework of two or three forms of treatment.

Methods

This study was approved by our Human Investigation Committee and written informed consent was obtained from each patient's next of kin. Over a period of 20 mo. from November 1994 to July 1996, we prospectively included all patients presenting with severe ARDS, whether this syndrome was the reason for their admission to our intensive care unit, or a secondary complication occurring after several days of hospitalisation. The severity criteria for inclusion were as follows: a Murray Lung Injury Score > 2.5 combined with a $\text{PaO}_2/\text{FiO}_2$ ratio < 170 after optimisation of the PEEP level. Exclusion criteria were major haemodynamic instability, pulmonary oedema due to heart failure and contraindications to NO, almitrine or prone positioning such as methaemoglobinaemia, severe pulmonary arterial hypertension or unstable spinal injury.

In addition to individually-adapted drug therapy such as antibiotic therapy, all patients were given midazolam

and fentanyl sedation without systematic neuromuscular relaxation. Monitoring included a thermodilution PA catheter (Opticath® Abbott, Mountain View, USA) and a radial artery catheter, and the lungs were ventilated in a pressure-regulated volume-controlled mode (PRVC, Siemens Servo 300®, Sweden) via oro- or nasotracheal intubation. After adequate fluid expansion, alveolar recruitment was performed up to a limit of + 14 cm H_2O PEEP (by steps of 2 cm H_2O), and in accordance with PaO_2 improvement, the best PEEP level was maintained constant at least three hours before the beginning of the study (H0) and throughout the duration of the protocol.

Mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), right atrial pressure (RAP) and pulmonary artery occlusion pressure (PAOP) were measured with a disposable quartz transducer connected to two calibrated pressure transducers (Monitoring Kit Transpac®, Abbott) and a monitoring system (Hewlett Packard 66S). Cardiac output was measured using thermodilution techniques, with serial injections of 5 ml dextrose 5% solution at room temperature, performed at random during the respiratory cycle, and was expressed as the mean of four measurements excluding the most extreme. Pulmonary vascular resistance indexes (PVRI), cardiac index (CI) and pulmonary shunt (Q_s/Q_t), were calculated using standard formulas. Arterial and mixed venous blood samples were collected anaerobically and immediately analysed by measuring PaO_2 , PaCO_2 , pH, total haemoglobin, haemoglobin oxygen saturation, and methaemoglobin concentration, using standard blood gas electrodes and spectrophotometry (Blood Gas Analyser IL 1630 and Co-Oximeter 482®, Instrumentation Laboratory, Paris).

Nitric oxide was administered continuously via the intake branch of the ventilator, after the humidifier, via a nitrogen flowmeter delivering flows in the range of 200–1500 $\text{ml}\cdot\text{min}^{-1}$. It was supplied from nitrogen cylinders containing a concentration of 225 ppm (CFPO, Air liquide, France). Inspired gas was sampled continuously 40 cm downstream of the NO injection, for monitoring of NO concentrations by an electrochemical measurement device (Polytrons®, Draeger, Germany), and 80 cm downstream for monitoring by an O_2 analyser (Ultima® Datex, Helsinki, Finland), of the FiO_2 actually administered. This monitoring enabled allowance for the effect of dilution that followed the entry of NO together with nitrogen as vector, when calculating $\text{PaO}_2/\text{FiO}_2$ ratios. The NO measurement apparatus was regularly calibrated using a nitric oxide tank with a reference nitrogen concentration.

As regards the practical arrangements for the prone position sessions, at least four hospital staff members turned patients into this position. One attended to the

FIGURE 1 Evolution of the $\text{PaO}_2/\text{FiO}_2$ ratio in groups A ($n = 9$), B ($n = 9$) and C ($n = 9$) between H0 and H7+12 (see legend of Table I for the treatment protocol). Groups A and B are pooled for the period H0-H3.

$P < 0.05$

Group C at H3 compared with group C at H0

Group A + B at H1 and H2 compared with Group A + B at H0

Group C at H1 and H2 compared with Group C at H0

Group A + B at H2 compared with group C at H2

Group A + B at H5 compared with group A + B at H0 and H3

Group C at H5 compared with group C at H0 and H3

Group A + B compared with group C at H + 5

Group C at H7 compared with group C at H5

Group A + B at H7 compared with group C at H7

FIGURE 2 Evolution of pulmonary shunt (Q_s/Q_t) in groups A ($n = 9$), B ($n = 9$) and C ($n = 9$) between H0 and H7+12. (see legend of Table I for the treatment protocol). Groups A and B are pooled for the period H0-H3.

$P < 0.05$

Group C at H3 compared with group C at H0

Group A + B at H1 and H2 compared with Group A + B at H0

Group C at H1 and H2 compared with Group C at H0

Group A + B compared with group C at H2

Group A + B at H5 compared with group A + B at H0

Group C at H5 compared with group C at H0

Group A + B compared with group C at H + 5

head and intubation probe. All patients had supports under the pelvis and shoulders.

Twenty-seven patients were included in this study and were divided into three groups (A, B and C) using a randomisation table. They inhaled NO for two hours, at concentrations of 5 and 10 ppm for one hour each (H 0-1 and 1-2). Then, one hour after inhalation stopped, they were placed in the prone position for four hours (Hs 3-7). From hours five to seven, Group B ($n = 9$) again inhaled NO at 10 ppm, whereas Group A ($n = 9$) did not. For Group C ($n = 9$) the procedure was the same as for Group B, but in addition, almitrine *iv* was perfused at $16 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ from Hour 0 until Hour 7 + 12 (Table I). Vascular loading and sympathomimetic treatments were maintained constant after optimisation of haemodynamic variables. Except for FiO_2 , ventilation parameters and their associated treatments were maintained constant throughout the procedure. Blood gas analysis and haemodynamic variables were recorded at H0, H1, H2, H3, H5, H7 as well as at four and twelve hours after returning to the supine position.

Means were compared with Wilcoxon, Mann-Whitney, Friedman and Kruskal-Wallis non-parametric tests. A Spearman test was used to search for a correlation between PAP at H0 and improvement of $\text{PaO}_2/\text{FiO}_2$ ratios with NO between H0 and H2. Percentages were compared with a Chi square test. A value of $P < 0.05$ was considered significant.

Results

During the study, two patients exhibiting the criteria of disease severity required for inclusion were excluded because of haemodynamic instability. Two of the patients included had skull injuries complicated by intracranial hypertension, which was monitored by an intraparenchymal pressure transducer (Camino Laboratories, San Diego, Ca). No change in intracranial pressure was recorded in a (strictly) horizontal prone position. The 27 patients studied had developed ARDS after primary bronchopneumopathy in 13 cases, multiple organ failure including peritonitis, pancreatitis, sepsis and mesenteric infarction in nine, pulmonary contusion in four and alveolar haemorrhage caused by lupus in one case. For 26 patients, the protocol was completed with PEEP main-

TABLE I Treatment protocol

	H0	H2	H3	H5	H7	H7+12
Group A	NO		PP	PP		
Group B	NO		PP	PP + NO		
Group C	NO + A	A	PP + A	PP + NO + A	A	

All patients inhaled NO 5 and 10 ppm for two hours. One hour later, they were placed in the prone position (PP) for four hours. Haemodynamic parameters and blood gases variables were measured at hours 0, 1, 2, 3, 5, 7, and at 4 and 12 hr after resumption of the supine position. Group B patients inhaled 10 ppm NO during the last 2 hours in the prone position. Group C patients were given the same treatment as those in Group B with, in addition, an almitrine (A) perfusion ($16 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$).

TABLE II Patients characteristics

	Group A n = 9	Group B n = 9	Group C n = 9
Age (yr)	52 ± 16	54 ± 18	59 ± 11
Weight (kg)	67 ± 28	74 ± 20	81 ± 17
Sex (M-F)	5/4	6/3	8/1
SAPS I	14 ± 4	14 ± 4	16 ± 5
Murray Score	2.8 ± 0.2	2.9 ± 0.3	2.9 ± 0.3
Aetiology of ARF			
(Pneumonia- MOF-			
Pulm. cont.-Haemorrhage)	4/3/2/0	4/2/2/1	5/4/0/0
Number of Deaths (n)	6	5	6

(mean ± SD)

ARF = acute respiratory failure;

Pulm. cont. = pulmonary contusion;

MOF = multiple organ failure;

SAPS = Simplified Acute Physiologic Score.

tained between 8 and 12 cmH₂O, and for one patient in Group C, at 14 cmH₂O. Nineteen patients had intensive sympathomimetic treatment with epinephrine, norepinephrine or >10 µg·kg⁻¹·min⁻¹ dopamine. The PRVC ventilation pressures always remained < 35 cm H₂O and it was never necessary to use permissive hypercapnia. Seventeen patients died in the intensive care department. The percentages of deaths according to ARDS aetiology were 54% for primary bronchopneumopathy and 78% for multiple organ failure.

Patients characteristics for each of the three groups are shown in Table II. The three groups were not different.

Effects of almitrine alone

The effects of treatment with almitrine only were assessed at Hour 3 in group C. There was an improvement in the PaO₂/FiO₂ and Qs/Qt ratios compared with Hour 0 (respectively +80 and -27%, *P* < 0.05). On the other hand there were no changes in MPAP values although they tended to rise faster in group C than in groups A+B between Hours 2 and 3. The other haemodynamic variables remained stable (see Table III). Among the patients who survived, none of those treated with almitrine presented any peripheral neuropathy

Effects of NO inhalation alone or combined with almitrine

The effects of NO inhalation alone were evaluated between H 0 and 2 in 18 patients, i.e., Groups A and B combined. Nitric oxide inhalation for one hour at a concentration of 5 ppm improved the PaO₂/FiO₂ ratio by 28%, reduced the Qs/Qt ratio by 9% and the PVR index by 25% (*P* < 0.05). After another hour of NO inhalation at 10 ppm, these parameters remained stable, at +25, -11 and -18% respectively, compared with H0. Nine patients were considered "non-responders" to NO because the PaO₂/FiO₂ ratio improved by < 20%. At H3, there was a decrease in the PaO₂/FiO₂ ratio (*P* < 0.05).

Of these 18 patients, five exhibited pulmonary artery hypertension exceeding 30 mmHg at H0. No correlation was found between PVRI at H0 and the improvement of PaO₂/FiO₂ ratios with NO between H0 and H2.

TABLE III Evolution of mean arterial pressure (MAP), heart rate (HR), cardiac index (CI), right atrial pressure (RAP) pulmonary artery occlusion pressure (PAOP) and mean pulmonary arterial pressure (MPAP) in groups A (n = 9), B (n = 9) and C (n = 9) between H0 and H7 (mean ± SD).

		H0	H1	H2	H3	H5	H7
MAP (mmHg)	A	90 ± 24	90 ± 16	87 ± 18	86 ± 14	88 ± 19	92 ± 20
	B	76 ± 15	81 ± 13	79 ± 12	84 ± 15	88 ± 14	85 ± 15
	C	87 ± 7	86 ± 17	77 ± 7	72 ± 13	78 ± 17	82 ± 12
HR (bpm)	A	101 ± 24	105 ± 33	100 ± 25	101 ± 26	102 ± 27	100 ± 24
	B	116 ± 25	112 ± 24	103 ± 24	100 ± 24	108 ± 30	113 ± 30
	C	99 ± 22	92 ± 14	99 ± 16	101 ± 15	98 ± 19	97 ± 17
CI (L·min·m ⁻²)	A	4.5 ± 1.1	4.7 ± 1	5.2 ± 1.5	5.4 ± 1.2	5.2 ± 0.9	5.4 ± 1.3
	B	4.7 ± 2.2	4.9 ± 1.8	4.5 ± 1.6	4 ± 1.9	4 ± 1.4	4.2 ± 1.6
	C	4.1 ± 1.8	4.2 ± 1.7	4.5 ± 1.5	4.8 ± 2.1	4.7 ± 2.2	5.2 ± 2.2
RAP (mmHg)	A	7 ± 3	7 ± 3.5	9.3 ± 4.2	10 ± 4.8	9.6 ± 5.3	9.3 ± 4.6
	B	5.2 ± 3	6 ± 3	6 ± 3.3	7 ± 4.5	8.6 ± 4.2	9.5 ± 4
	C	8 ± 1.8	8 ± 1.7	7.5 ± 3.2	6.7 ± 2.2	9.5 ± 3.4	8.6 ± 2.2
PAOP (mmHg)	A	10.5 ± 3.8	12.5 ± 4.3	13.2 ± 3.2	14.6 ± 5	14 ± 5.5	13.2 ± 4.4
	B	12 ± 7	10.3 ± 3.5	9.8 ± 5	12.3 ± 6	11 ± 4.4	11 ± 3.4
	C	13.3 ± 6.1	14.2 ± 8.5	16.8 ± 8.5	15 ± 8.2	17 ± 7.9	15.5 ± 6
MPAP (mmHg)	A	27 ± 10	24 ± 4	26 ± 5	28 ± 8	29 ± 9	28 ± 9
	B	26 ± 7	23 ± 7	24 ± 5	26 ± 7	28 ± 8	26 ± 7
	C	32 ± 9	31 ± 8	29 ± 6	33 ± 9	35 ± 7	32 ± 6

The effects of combined treatment with NO and almitrine were evaluated in the nine group C patients at H2. In this group, the $\text{PaO}_2/\text{FiO}_2$ ratio was improved by 153% and the Qs/Qt ratio diminished by 28% ($P < 0.05$). Comparison of groups A+B and C showed that there was a greater improvement in oxygenation and in the Qs/Qt ratio when NO and almitrine treatment were combined than when NO was used alone ($P < 0.05$). Whether or not NO inhalation was combined with almitrine, it did not modify general haemodynamics, i.e., heart rate, MAP and CI, or give rise to any manifestation of excess administration of NO, as assessed from measurement of the expired NO_2 fraction which never exceeded 0.3 ppm, or methaemoglobin, concentration always $< 1\%$.

Effects of Prone Positioning alone or combined with almitrine

In all three groups, the first two hours in the prone position improved the $\text{PaO}_2/\text{FiO}_2$ ratio. At H5, this ratio improved in groups A and B combined by 88% compared with H0, and by 79% compared with H3 ($P < 0.05$). At these times, there were concomitant reductions in the Qs/Qt ratio of 25 and 15% respectively, which were only significant compared with H0 ($P < 0.05$). All haemodynamic parameters remained stable. Fourteen patients displayed improvement of $> 20\%$ in $\text{PaO}_2/\text{FiO}_2$ ratio and were considered as "Prone position responders." The prone position, improved the $\text{PaO}_2/\text{FiO}_2$ ratio by 92% in the nine patients which were considered "non-responders" to NO. Only two patients responded to neither of these two treatments.

After return to the supine position, there was a gradual decline in the oxygenation variables, with a return at H7 +12 to the levels measured at H0. Individual assessments showed that $\text{PaO}_2/\text{FiO}_2$ ratio after four hours remained 20% higher than at H0 in 12 patients. Six patients exhibited fast degradation of this ratio.

The effect of combining prone positioning with almitrine administration was evaluated in Group C. At H5, the $\text{PaO}_2/\text{FiO}_2$ ratio improved by 132% compared with H0, but only by 53% ($P < 0.05$) compared with H3, due to the effects of almitrine alone at this time. At H5, the Qs/Qt ratio was 28% lower than at H0 ($P < 0.05$) and remained stable in relation to its H3 level. At H5, the $\text{PaO}_2/\text{FiO}_2$ ratio in group A+B differed from the Group C ratio ($P < 0.05$). Prone positioning did not change any of the haemodynamic variables.

As regards specific complications resulting from prone positioning, one patient experienced sudden obstruction of the endotracheal tube which necessitat-

ed immediate supine positioning for emergency re-intubation. Facial oedema was common, but regressed after a few hours in the supine position.

Combined effects of NO inhalation and prone positioning

The effects of combining NO and prone positioning were appreciated by comparing the values measured at H7 in Groups A and B, i.e., in two unpaired populations of nine patients each. In Group A, two extra hours in the prone position did not, lead to any additional increase in oxygenation or change in Qs/Qt ratio in relation to that already obtained between H3 and 5. In Group B, the $\text{PaO}_2/\text{FiO}_2$ ratio improved slightly by 17%. The haemodynamic parameters remained unchanged.

Combined effects of NO inhalation, prone positioning and almitrine

The effects of combining NO inhalation, prone positioning and almitrine treatment were assessed in Group C : at H7, the $\text{PaO}_2/\text{FiO}_2$ and Qs/Qt ratios respectively improved by +84 and -15% compared with H5. The improvement in $\text{PaO}_2/\text{FiO}_2$ only was significant. The other haemodynamic variables were unchanged. One patient who displayed no improvement died before H24, of extensive bilateral pneumopathy.

Discussion

All symptomatic treatments tested improved arterial oxygenation during severe ARDS. They differed significantly and can be classified in increasing order of effectiveness: $\text{NO} < \text{almitrine or PP} < \text{NO} + \text{almitrine or PP} + \text{almitrine} < \text{NO} + \text{almitrine} + \text{PP}$.

The main inclusion criteria were more selective than in many similar studies as we chose a $\text{PaO}_2/\text{FiO}_2$ ratio < 170 for a PEEP level of ≥ 8 cm H_2O . The shortest possible periods of exposure were chosen so that spontaneous evolution of the disease would hamper evaluation of treatment effectiveness as little as possible. Thus, the effects of two hours of NO inhalation were compared with those of two hours in the prone position, because, depending on the authors, the optimal effects of these two treatments are respectively obtained after 8 to 12 min¹⁰ and after 60 to 120 min.¹¹ The order of treatment administration was determined by the absence of any residual effect 30 min after the end of NO inhalation.¹² As regards the dose of NO, we chose not to exceed 10 ppm because, although some investigations found it advantageous to use higher proportions for septic patients,¹³ most authors have reported a dose-dependent effect for up to 2 to 10 ppm but no benefit beyond this.^{14,15} Almitrine was administered at the dose advocated for this treatment at the time this study start-

ed. We administered it throughout the protocol, due to its long half-life.¹⁶ In accordance with previous studies,¹⁷ a 20% improvement of $\text{PaO}_2/\text{FiO}_2$ ratio was chosen to define those patients who responded well to a treatment.

Nitric oxide inhalation reduces pulmonary artery pressure and improves oxygenation by reducing right-to-left shunt, due to selective vasodilatation of the pulmonary vessels located in ventilated lung areas. In our series, the overall improvement in oxygenation was small, compared with the 30 to 50% reported in some studies.¹⁸ It should be stressed that, unlike many other authors, we did not select the "good responders." The percentage of good responders we found is close to that generally reported.^{6,14} The absence of any effect on general haemodynamics with this mode of administration is explained by the rapid metabolism of NO which combines with haemoglobin. The presence of severe PA hypertension has been reported by some authors to be a predictive factor of especially marked sensitivity to NO.¹⁹ The lack of correlation between initial PAP and the efficacy of NO in our patients can be explained by the fact that, overall, the population did not present any major PA hypertension at the time of inclusion. For the 18 patients in groups A+B, MPAP was 26 ± 8 mmHg at H 0, whereas it was 35 ± 2 mmHg in the patients from the study by Rossaint *et al.* who exhibited an 83% response rate.⁶

Almitrine, a respiratory analeptic, can also reduce the shunt by increasing hypoxic pulmonary vasoconstriction in poorly ventilated areas.²⁰ At H 3 it had as great an action on oxygenation as that of prone positioning. The improvement obtained at H 7 + 4 and H 7 + 12, was not retained because this could be attributed in part to the residual effects of prone positioning. We found no rise in MPAP in group C at H 3 or H 5 in association with the prone position. However, it is difficult to individualise the effect of this treatment in itself and the consequences of improved hypoxia for the smooth muscle vasculature. Nor did we find any systemic haemodynamic changes. This is often the case as reported in the literature, apart from some studies reporting a rise in heart rate and cardiac output.²¹

The increase of 153% in the $\text{PaO}_2/\text{FiO}_2$ ratio strongly favoured the combination of almitrine with NO inhalation. The synergistic effect of these treatments on the improvement of oxygenation has already been the subject of several investigations.^{22,23} Using the same doses of almitrine, Lu *et al.*²⁴ found, in a similar population, an improvement of 150% in the $\text{PaO}_2/\text{FiO}_2$ ratio after one hour of exposure to 1.5 ppm of NO. Law-Koune *et al.*²⁵ showed that when this happened, pulmonary vascular resistance remained unchanged.

The evolution we observed in $\text{PaO}_2/\text{FiO}_2$ ratio with

the prone position was consistent with most results published which report a 50 to 100% improvement in oxygenation by one hour that is not sustained,^{11,31} an absence of haemodynamic repercussion, almost constant effectiveness, and a beneficial duration in one of two cases for several hours after terminating prone positioning. As Dubois *et al.*³² we distinguished a category of patient described as prone position-dependent, who exhibited fast impairment of blood gas parameters after returning to the supine position. Turning patients from the supine to the prone position improves the $\text{PaO}_2/\text{FiO}_2$ ratio by generating transpulmonary pressure sufficient to exceed airway opening pressure in dorsal lung regions where atelectasis, shunt and ventilation perfusion heterogeneity are most severe.²⁶ In obese patients, during general anaesthesia, it increases functional residual capacity and lung compliance without changing total respiratory system compliance and resistance.²⁷ Regional perfusion becomes more uniform due to redistribution along gravitational gradient toward better ventilated areas. If chest and pelvic supports are used, prone positioning improves diaphragm kinetics by causing an unloading of the abdominal viscera²⁸ without adversely affecting ventral lung regions. Finally, a major part of its action is explained by the bronchial secretions draining effect. This improvement was confirmed by CT scan, which disclosed a decrease of 30 to 50% in the number of pulmonary segments with large infiltrates. This decrease persisted for several hours after the return to the supine position.^{29,30} Prone positioning and almitrine exerted a potentiation, which was not found to be significant with the association of NO inhalation + prone positioning.

The best results were recorded with triple therapy of NO inhalation, prone positioning and almitrine. This association had no deleterious haemodynamic effects. This can probably be explained by the complementary nature of the modes of action of each of these treatments. The increase in perfusion of well-ventilated lung areas due to the action of NO and the accentuation of hypoxic pulmonary vasoconstriction by almitrine make it possible to improve the ventilation/perfusion ratios, while the main effect of the prone position is to eliminate some posterior atelectasis.

These results provide the basis for therapeutic recommendations. The addition of almitrine improves the effectiveness of NO inhalation, and it seems advisable to combine the two for a short period. After a few days, one cannot eliminate the risk of neuropathy as a reaction to almitrine. Prone positioning is a good alternative which is effective in nearly 80% of cases and may prove indispensable for certain patients who do not respond to NO. Unfortunately, for trophic rea-

sons, it is a discontinuous form of treatment. Patients with the most severe lesions may benefit from a combination of the three treatments in order to limit the toxic effects of a high FiO_2 or PEEP level.

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