Comparison of the effects of intravenous almitrine and positive end-expiratory pressure on pulmonary gas exchange in adult respiratory distress syndrome

J-F. Prost, P. Desché, F. Jardin, A. Margairaz

ABSTRACT: The effects of almitrine on pulmonary gas exchange and haemodynamics were compared to those of positive end-expiratory pressure (PEEP) in 10 patients with a severe adult respiratory distress syndrome (ARDS) who required continuous mechanical ventilation. Haemodynamic and gas exchange measurements were made before and after 30 min of PEEP at a level of 10 cmH₂O, then 30 min later, before and at the end of the intravenous infusion of almitrine at a dose of 0.25 mg·kg⁻¹·h⁻¹. There was no significant difference between baseline gas exchange and haemodynamic parameters.

PEEP and almitrine increased Pao₂ (p=0.001) from 10.9 to 12.6 kPa and from 10.6 to 12.6 kPa (1 kPa = 7.5 mmHg), respectively, and ratio of venous admixture to total blood flow (Qs/Qt) decreased (p<0.001) from 34 to 29% and from 33 to 29%, respectively, the effects of PEEP and almitrine being not significantly different. Neither PEEP nor almitrine caused a significant change in arterial carbon dioxide tension (Paco₂).

The haemodynamic parameters did not change significantly with almitrine, whereas mean systemic arterial pressure decreased from 85.4 to 81.1 mmHg (p<0.05) with PEEP.

These results are consistent with the hypothesis that both treatments improve ventilation/perfusion (V̇A/Q) distributions, by an increase in functional residual capacity in the case of PEEP and a redistribution of pulmonary perfusion in the case of almitrine.


Almitrine, a piperazine derivative, has been shown to significantly increase arterial oxygen tension (Pao₂) and decrease arterial carbon dioxide tension (Paco₂) in patients with chronic obstructive pulmonary disease (COPD) [1, 2], these beneficial effects being sustained for at least one year [3, 4]. The exact mechanism of this improvement in pulmonary gas exchange is not yet established with certainty. As initially demonstrated in animals [5, 6], this effect may result from an increase in ventilation due to sustained stimulation of peripheral chemoreceptors. However, recent studies of ventilation/perfusion (V̇A/Q) distributions in patients with COPD using either isotopic [7, 8] or multiple inert gas elimination [9, 10] techniques have demonstrated that almitrine improves pulmonary gas exchange by reducing the V̇A/Q mismatching, without any increase in minute ventilation.

The adult respiratory distress syndrome (ARDS) is a common and often lethal disorder in which intrapulmonary shunting with increased blood flow to lung areas with low V̇A/Q ratios is the main cause of severe hypoxaemia [11]. In these patients, positive end-expiratory pressure (PEEP) has been shown to reduce both shunt and perfusion to low V̇A/Q regions [12] and is now considered as the standard therapeutic intervention to improve gas exchange. However, Reyes and co-workers [13, 14] recently demonstrated that a significant increase in Pao₂ with a significant decrease in ratio of venous admixture to total blood flow (Qs/Qt) could be obtained with intravenous administration of almitrine to patients with acute respiratory failure [13] or ARDS [14]. As shown by the multiple inert gas elimination technique, this improvement in pulmonary gas exchange was related to a reduction in the V̇A/Q inequalities present in ARDS [14]. In both studies, most patients were ventilated with a PEEP between 6 and 15 cmH₂O.

The aim of the present study was to assess the effects of a single dose of almitrine on pulmonary gas exchange and haemodynamics in comparison with those induced by a PEEP of 10 cmH₂O in patients with ARDS.
Methods

Patients

Ten patients with ARDS who required controlled mechanical ventilation were studied. This group consisted of six men and four women ranging in age from 21–68 years (mean, 41.4 yrs). The diagnosis of ARDS was based on the following criteria: severe hypoxaemia with PaO₂ less than 8 kPa (1 kPa = 7.5 mmHg) on a mean inspired oxygen concentration of 50% or higher, diffuse pulmonary opacities on chest radiograph, absence of left ventricular failure as documented by pulmonary capillary wedge pressure at end-expiration of less than 15 mmHg and a compatible underlying disease. Respiratory failure followed aspiration pneumonia in six cases, abdominal sepsis in two cases, overperfusion and sepsis in one case and bilateral lung contusion in one case. None of the patients had a clinical history of cardiac or pulmonary disease. Informed consent was obtained from patients' next-of-kin.

Study design

The study was performed between the second and the fourth day of respiratory assistance, all of the patients being stable for at least the preceding four hours. At this time, patients were sedated with a constant intravenous infusion of haloperidol and phenoperidine, and mechanically ventilated by a nasotracheal tube using a volume-controlled ventilator (Bourns Bear One or ATM CPU). Ventilatory pattern was set to obtain normal pHa and PacO₂ and an arterial oxygen saturation, at zero end-expiratory pressure (ZEEP), close to 90% (mean inspired oxygen concentration, 55%). Except for the end-expiratory pressure, the ventilatory pattern was not modified throughout the study. Likewise, if before commencement of the study inotropic agents were administered for maintaining cardiovascular stability, their infusion rate was kept constant.

Patients were studied in the supine position. Due to the long elimination half-life of almitrine, ranging from 116–140 h [15], the study periods with PEEP or almitrine could not be performed in a randomized order. Therefore, for each patient the study protocol was divided into the following four successive periods of thirty minutes: a first equilibration period with controlled ventilation at ZEEP (control 1), then a period during which a PEEP of 10 cmH₂O was applied, a second equilibration period with controlled ventilation at ZEEP (control 2) allowing a progressive return to the baseline state, and finally a period during which almitrine was infused at a dose of 0.25 mg·kg⁻¹ over 30 min. At the end of each period haemodynamic and gas exchange parameters were measured.

Measurements

Haemodynamic and gas exchange measurements were performed as previously described [16]. Mean systemic arterial (MSAP), mean pulmonary arterial (MPAP) and pulmonary capillary wedge (PCWP) pressures at end-expiration were measured from radial Vygon Leadercath and pulmonary Swan-Ganz catheters inserted percutaneously, and connected to Hewlett-Packard pressure transducers positioned at the midaxillary level, with the use of atmospheric pressure as a zero reference level. Cardiac output was measured by the thermodilution technique (Edwards cardiac output Computer 9520), the result being the mean of three serial determinations. Partial pressures of oxygen and carbon dioxide from arterial (PaO₂, PaC O₂) and mixed venous blood (PVO₂, PCO₂) samples were determined using a Radiometer Anaerobic Oximeter and corrected for the patient's temperature. Haemoglobin oxygen saturation was measured with a Radiometer Spectrophotometer.

From these measurements, the following parameters were calculated according to standard formulae:
- pulmonary vascular resistance (PVR) PVR = MPAP - PCWP/CI, where CI is the cardiac index;
- ratio of venous admixture to total blood flow (Qs/Qt): Qs/Qt = (CVO₂ - CAO₂) / (CVO₂ - CVŌ) x 100, where CVO₂, CAO₂ and CVŌ are the pulmonary capillary, arterial and mixed venous oxygen content, respectively.

<table>
<thead>
<tr>
<th>Table 1. - Blood gases and haemodynamics before and after 30 min of PEEP and almitrine infusion in 10 ARDS patients</th>
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<tr>
<td><strong>PEEP 10 cmH₂O</strong></td>
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<tr>
<td>PaO₂, kPa</td>
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<td>PacO₂, kPa</td>
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<td>Qs/Qt, %</td>
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<td>PVR, mmHg·min⁻¹</td>
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**p<0.05; ***p=0.001; ***p<0.001 in comparison with respective baseline values. ¹: p=0.05 in comparison with almitrine. PaO₂, PacO₂: arterial oxygen and carbon dioxide partial pressures, respectively. (1 kPa = 7.5 mmHg); Qs/Qt: ratio of venous admixture of total blood flow; CI: cardiac index; MSAP, MPAP: mean systemic and pulmonary arterial pressures, respectively; PVR: pulmonary vascular resistance. Mean±SEM.
Baseline values at the end of both control 1 and control 2 periods were compared using a two-way analysis of variance and effects of PEEP and almitrine were compared using a three-way analysis of variance [17].

Results

Results, expressed as mean±SEM, are shown in table 1. For all of the gas exchange and haemodynamic parameters, there was no significant difference between baseline values at the end of both control 1 (just before PEEP) and control 2 (just before almitrine infusion) periods.

Compared with respective baseline values, both PEEP and almitrine induced an increase (p<0.001) in Pao2 of 1.7 and 2.0 kPa (1 kPa = 7.5 mmHg), respectively, associated in both cases with a decrease (p<0.001) in Qs/Qt of 5.4 and 4.1%, respectively. The effects of almitrine on Pao2 and Qs/Qt were not significantly different from those induced by PEEP. Neither PEEP nor almitrine caused a significant change in Paco2.

PEEP produced a moderate but significant decrease in MSAP (-4.3 mmHg, p<0.05). In contrast, almitrine did not significantly alter any of the haemodynamic parameters. The effects of PEEP and almitrine on MSAP were significantly different (p=0.05).

No adverse side-effect was observed during or after the administration of almitrine.

Discussion

At present, this study is the first to compare the effects of almitrine to those of PEEP in patients with ARDS. Our results show that intravenously administered almitrine increased Pao2 and decreased venous admixture in these patients, to the same extent as a PEEP of 10 cmH2O, with no significant changes in mean systemic and pulmonary arterial pressures and cardiac output. Minute ventilation and inspired oxygen concentration were maintained constant throughout the study. Therefore, these results are consistent with the hypothesis that almitrine improves gas exchange by reducing V/Q inequalities.

We studied patients suffering from a severe ARDS, as shown by a mean Qs/Qt of 34.2% at the end of the first equilibration period, decreasing to 28.8% with a PEEP of 10 cmH2O. Due to the long elimination half-life of almitrine, ranging from 116-140 h [15], the study periods with PEEP or almitrine could not be performed in a randomized order. Therefore, almitrine was administered to each patient after a second equilibration period of 30 min, following the study period with PEEP. Baseline measurements were repeated just before the administration of almitrine. As shown by the absence of significant difference between baseline values measured just before PEEP and almitrine, there was no carry-over effect of PEEP and almitrine, there was no carry-over effect of PEEP and almitrine.

The rise in Pao2 following almitrine administration to subjects mechanically ventilated was first reported by TENAILLON et al. [18] in COPD patients suffering from an acute exacerbation of respiratory failure. This finding was later confirmed by CASTAING et al. [10] who demonstrated, in accordance with previous studies [7, 9], that almitrine improved the matching of pulmonary blood flow to ventilation in such patients. In contrast with the numerous reports on the effects of almitrine in COPD patients and in spite of the hypothesis that this drug may improve V/Q distributions, few studies have been performed in ARDS patients. REYES et al. [13] administered a single dose of 0.5 mg·kg-1 of almitrine intravenously over 30 min to eight patients with acute respiratory failure secondary to sepsis or shock. Six of these patients were ventilated with a PEEP of 6-12 cmH2O. Results demonstrated a mean increase in Pao2 of 43 mmHg and a mean decrease in Qs/Qt of 5% at the end of almitrine administration. In a second study, REYES and co-workers [14] administered the same dose to nine patients with ARDS, seven of whom being ventilated with a PEEP of 10-15 cmH2O. Almitrine produced a mean increase in Pao2 of 60 mmHg and a mean decrease in Qs/Qt of 8%. In addition, as shown by the inert gas measurements performed in this study, these effects occurred in parallel with a reduction in the V/Q inequalities present in ARDS. Our results are in accordance with these data, although we observed smaller changes in both Pao2 and Qs/Qt. This might be explained by differences in patients and also by differences in doses, the dose we used being half that utilized by REYES and co-workers in their studies [13, 14].

The effectiveness of PEEP is primarily related to an increase in functional residual capacity with the opening of previously collapsed airways or alveoli [12]. In contrast, the mechanism by which almitrine improves V/Q distribution is still poorly understood. Theoretically, it may involve a redistribution of ventilation, perfusion or both. A redistribution of ventilation in the absence of changes in external ventilation has been suggested as a mechanism for the improved gas exchange produced by almitrine [19]. However, this mechanism cannot explain our results obtained in sedated and mechanically ventilated patients. On the other hand, experimental studies in rats have shown that almitrine could have a beneficial effect on gas exchange by increasing thoracic gas volume [20]. However, this has not so far been detected in patients, and further studies are required to investigate this possible mechanism of action of almitrine. Therefore, the most probable explanation is a redistribution of perfusion.

In a model of global hypoxia in closed-chest dogs with normal lungs, ROMALDINI et al. [21] found that the increase in PVR induced by almitrine was greater during hypoxic ventilation than during normoxic ventilation, suggesting that the drug may enhance hypoxic pulmonary vasoconstriction. On the other hand, according to results obtained in a canine model of regional hypoxia [22] and in dogs with experimental ARDS [23], the suggestion has been made that almitrine may induce a
pulmonary vasoconstriction independently of the level of the partial pressure of oxygen. These discrepancies might be explained by differences in experimental models as well as by differences in doses. In a canine left lower lobe preparation, Nakashin et al. [24] found that the hypoxic pulmonary vasoconstriction was enhanced by a low dose of almitrine whereas it was attenuated by a high dose. In accordance with these results, Mélot et al. [25], using a low dose of 4 \( \mu g \cdot kg^{-1} \cdot \text{min}^{-1} \) in normal subjects, have recently reported that the improvement in PaO, induced by almitrine during hypoxic and normoxic conditions occurred simultaneously with an increase in both MPAP and PVR, whereas no change in pulmonary haemodynamics was observed upon 100% \( O_2 \) breathing. The enhancement of hypoxic pulmonary vasoconstriction by almitrine is also strongly suggested by the decrease in blood flow to low \( V_A / Q \) hypoxic lung regions demonstrated in COPD patients under controlled mechanical ventilation [10]. This increase in pulmonary vascular tone induced by almitrine may result from either a stimulation of peripheral chemoreceptors [26] or a direct effect on pulmonary vessels [27]. With a dose of 0.5 mg kg\(^{-1}\), a small but significant increase in MPAP was observed at the end of almitrine infusion in the two studies conducted by Rayss and co-workers [13, 14]. The lack of significant change in both MPAP and PVR in our study might be explained either by the small number of patients or by the use of a lower dose of almitrine. In addition, the vasoconstriction induced by almitrine could be either limited, with local vascular adjustments not detectable by using a Swan-Ganz catheter, or compensated by a capillary recruitment, as has been demonstrated in experimental studies of hypoxic vasoconstriction [28].

In a previous study [29], the decrease in MSAP induced by PEEP was only significant at levels of 15 cmH\(_2\)O or more. In accordance with these results, we observed a moderate decrease in MSAP with a PEEP of 10 cmH\(_2\)O. However, compared to almitrine, this change in MSAP was significant.

In conclusion, we found that a low dose of almitrine improved pulmonary gas exchange in patients with ARDS to the same extent as a PEEP of 10 cmH\(_2\)O, without any significant change in systemic and pulmonary haemodynamics. However, pulmonary hypertension caused by an increased PVR is an early and progressive feature of ARDS [30] and morphometric studies have shown that, in addition to leucocyte plugging and microthrombosis, ARDS is characterized by partial or complete disruption of the pulmonary precapillary arterial bed [31]. Whether the increase in pulmonary vascular tone induced by almitrine has a deleterious effect in the evolution of these microvascular lesions is not known. In addition, results of previous studies have shown that in this setting, the improvement in pulmonary gas exchange induced by almitrine is of short duration, lasting less than one hour after infusion was stopped [13, 14]. However, Rekik et al. [32] have recently reported that an intravenous infusion of a low dose of almitrine over a 48 h period to patients with severe ARDS durably improved pulmonary gas exchange without any significant decrease in right ventricular function. Therefore, although these results suggest that almitrine may be useful in the management of such patients, further studies are required in order to establish dose-effect relationships and to determine the haemodynamic tolerance of a repeated administration.

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References

Comparaison entre les effets de l'almitrine i.v. et ceux de la pression positive en fin d'expiration (PEEP) sur les échanges gazeux dans le syndrome de détresse respiratoire aiguë de l'adulte (ARDS). J.-F. Frott, P. Desché, F. Jardín, A. Margairaz.

RÉSUMÉ : Les effets de l'almitrine sur les échanges gazeux et l'hémodynamique pulmonaires ont été comparés à ceux de la PEEP chez 10 patients atteints d'ARDS sévère nécessitant une ventilation mécanique continue. Les mesures ont été faites avant et après 30 minutes de PEEP au niveau de 10 cmH2O, puis 30 minutes plus tard, avant et après la fin d'une perfusion intraveineuse d'almitrine à la dose de 0.25 mg·kg-1·min-1 en 30 minutes. Il n'y avait pas de différence significative entre les valeurs basales des échanges gazeux et de l'hémodynamique. PEEP et almitrine ont augmenté la Pao2 respectivement de 10.9 à 12.6 kPa et de 10.6 à 12.6 kPa (1 kPa=7.5 mmHg) (p<0.001), alors que Qs/Qt baisait respectivement de 34 à 29% et de 33 à 29% (p<0.001). Il n'y a pas de différence significative entre les effets de PEEP et d'almitrine. Ni PEEP, ni almitrine, n'entraînent de modification significative de l'hémodynamique. Les paramètres hémodynamiques ne se modifient pas significativement sous l'effet de l'almitrine, alors que la pression artérielle systolique moyenne baisse de 85.4 à 81.1 mmHg (p<0.05) sous PEEP. Ces résultats sont compatibles avec l'hypothèse selon laquelle les deux traitements améliorent les distributions de V/A/Q, la PEEP en augmentant la CRF et l'almitrine en provoquant une redistribution de la perfusion pulmonaire. Eur Respir J, 1991, 4, 683-687.