Cardiopulmonary Effects of a Single Oral Dose of Almitrine at Rest and on Exercise in Patients with Hypoxic Chronic Airflow Obstruction

Gérald Simonneau, M.D.; Michel Meignan, M.D.; André Denjean, M.D.; Bernadette Raffestin, M.D.; Alain Harf, M.D.; and Jean-François Prost, M.D.

Almitrine, a new triazine derivative, was studied in a double-blind, randomized, parallel study in 16 patients with hypoxic chronic airflow obstruction (eight almitrine and eight placebo). At rest, compared to placebo, a 3 mg/kg single dose of almitrine given orally significantly increased the partial pressure of oxygen (mean increase: +12.0 ± SEM 2.1 mm Hg, p < 0.001) and decreased the partial pressure of carbon dioxide (mean decrease: −6.0 ± 0.7 mm Hg, p < 0.001); this improvement in arterial blood gases persisted on exercise. The lack of significant change in ventilation and the decrease in the alveolar-arterial oxygen gradient (mean decrease = 10.0 ± 1.9 mm Hg; p < 0.001) at rest suggests a change in the distribution of the ventilation-perfusion ratio in the lung, such a change was confirmed by a krypton 81m isotopic study. Pulmonary hemodynamic responses were studied at rest and on exercise; a significant but slight increase in mean pulmonary artery pressure at rest (+4.0 ± 1.5 mm Hg, p < 0.05) was found.

Correction of hypoxemia is beneficial for patients with chronic airflow obstruction. This can be achieved by 12-hour, or even better by 24-hour continuous oxygen therapy, but such therapy is both constraining for the patient and expensive. A long-acting drug with the same effect on arterial blood gases would be of obvious therapeutic value. Almitrine (almitrine bismesylate), a new triazine derivative, could be such a drug, since it has shown analeptic activity with subsequent improvement in blood gas levels in animals, normal men and bronchitis patients. With small doses of oral almitrine, it has been demonstrated in bronchitis patients that the improvement in blood gases does not depend upon an increase in external ventilation. Furthermore, in chronic bronchitis patients treated for acute respiratory failure with fixed external ventilation, the partial pressure of oxygen increases significantly following intravenous administration of almitrine. These observations suggest that the improvement in pulmonary gas exchange is not entirely accounted for by the analeptic effect of almitrine and that this drug is able to improve the distribution of ventilation/perfusion (VA/Q) within diseased lungs. Among the reported side-effects of almitrine, an increase in resting pulmonary arterial pressure and vascular resistance have been noted with large intravenous doses.

The present work was undertaken with several objectives: 1) a study of blood gases, ventilation and hemodynamics at rest and on exercise in order to confirm the activity of oral almitrine on gas exchange and to examine the role of the increase in ventilation and the increase in pulmonary arterial pressure; 2) an isotopic study at rest to examine changes in VA/Q ratios and to confirm changes in ventilation and gas exchange.

MATERIAL AND METHODS

Subjects

Sixteen patients (age range 41 to 76 years) were studied. The criteria for inclusion in the study were: 1) diagnosis of severe chronic airflow obstruction caused by chronic bronchitis, substantiated by both history and previous assessment of lung function; 2) chronic hypoxemia (PaO₂ < 70 mm Hg in room air) associated with normocapnia in five patients or chronic hypercapnia in the 11 others; 3) absence of bronchial asthma or any condition that would affect the left heart. Associated restrictive lung disease was also present in three patients with total lung capacity equal to 56, 70 and 71 percent of predicted values. All patients were in a stable clinical state as assessed by lack of changes in body weight and arterial blood gas levels during the month preceding the study. Informed consent was obtained from every patient.

Procedures

Blood gas, ventilation and hemodynamic studies of both almitrine and placebo were carried out separately from isotopic studies, but using the same order of randomization. Blood gases, ventilation and pulmonary hemodynamics were studied at rest and on exercise according to a double-blind, randomized parallel trial. The almitrine (A, n = 8) and placebo (P, n = 8) groups were not statistically different for age (A = 63 ± 2, P = 60 ± 2 years), basal arterial blood gases (A = PaO₂ 62 ± 2; PaCO₂ 46 ± 2 mm Hg; P = PaO₂ 59 ± 2; PaCO₂ 46 ± 2 mm Hg) and forced expiratory volume in one second (A = 1.01 ± 0.19; P = 1.02 ± 0.10 L s⁻¹).
The isotopic study of regional lung function with krypton 81m was carried out at rest in seven of eight patients in the placebo group and five of eight in the almitrine group, either 48 hours before or after the blood gas, ventilation and hemodynamic studies.

Blood Gas, Ventilation and Hemodynamic Study

Patients were semi-recumbent and breathed room air throughout the study. A thermistor tip catheter (Edwards Laboratories) was introduced percutaneously and floated to the correct position. An indwelling No 3 French arterial catheter was inserted into the radial artery. Details on pressure recordings, determination of cardiac output by the thermodilution method and analysis of blood gases have been reported in more detail previously.5

The patients breathed room air through a mouthpiece attached to a t-tube valve; expired gas, after passing through a mixing box, was collected in a Tissot spirometer and external ventilation (V̇e) continuously recorded. Mixed expired PO2 (FeO2) and CO2 (FeCO2) were obtained by analyzing with a mass spectrometer (Centronic MG 2000) and the expired air collected in the Tissot spirometer. Partial pressures of O2 and CO2 monitored at the mouth with the mass spectrometer were recorded and used to calculate respiratory rate and end tidal PO2 (Pet O2) and Pco2 (PetCO2). Mean alveolar PO2 (Pao2) and Pco2 (Paco2) were taken to be the coordinates of the point where single breath tracings of instantaneous expired O2 and CO2 crossed the superimposed mixed expired line (RE) drawn between inspiratory and mixed expired O2 and CO2 points.6 The ratio of physiologic dead space to tidal volume (Vd/Vt), the ratio of venous admixture to total blood flow (Qs/Qt), the ratio of O2 and CO2 alveolar-arterial gradients (P-AO2, Pa-AO2), O2 consumption (VO2), and respiratory exchange ratio (VCO2/VO2) were computed with classic formulae.

In every patient, four different trials were carried out sequentially: a control trial without treatment at rest (Rc) and during mild exercise (20 to 40 W) in semi-recumbent position over six min (Ec) and a test trial three hours after the administration of either almitrine (3 mg/kg) (Rs) or placebo (Rp) at rest and during a second identical exercise (Ea or Ep).

In each trial, measurements began only after end-tidal Pco2 had reached a steady state and lasted approximately three minutes, during which the following measurements were obtained sequentially: intravascular pressures, a cluster of three thermodilution curves, sample of arterial and mixed venous blood and finally a second cluster of three thermodilution curves. Collection of expired gases and sampling of expired gas at the mouth were also carried out over the same three min.

Finally, a blood sample was withdrawn during periods Ra or Rp (three hours after the administration of treatment) to measure the concentration of almitrine in plasma.

Isotopic Study

Measurements: Patients were studied in a semi-recumbent position with their back to a gamma camera (Opticamera-CGR France) equipped with a medium energy collimator and linked to a computer (Simis 3, Informatek, France). After arterial sampling for Po2 and PCO2 measurements, a ventilation lung scan was performed, the subject breathed an air-krypton 81m mixture at a flow of 1 L·min⁻¹ through a face mask, and a posterior view of the radioactivity distribution was recorded. After the fast decay of lung radioactivity and without moving the patient, a perfusion scan was performed by infusing krypton, eluted with a 5 percent dextrose solution, into an antecubital vein at a rate of 10 ml/min. Two hundred thousand counts for both ventilation and perfusion were acquired in the computer memory on a 64 x 64 matrix form and stored on magnetic disks. The dose delivered to the lung was about 3.5 mRads. External ventilation was measured at the same time by collecting expired gases in a Douglas bag. The total time required for a complete isotopic study at rest did not exceed ten min. The isotopic study was carried out twice in each subject: control isotopic study (Risoc) and after administration of almitrine (3 mg/kg) (Risop) or placebo (Risop).

Computation of Regional Ventilation/Perfusion Ratios (V̇a/Q̇)

The rationale underlying the use of short-lived isotopes and the details of computations have been thoroughly discussed in a previous publication.25 Images were displayed on a TV screen and the outlines of the two lungs were drawn. The region corresponding to the radioactivity in the subclavian vein during constant infusion was subtracted. The number of counts in each lung was normalized for the total counts over both lungs on ventilation and perfusion scans. Each lung surface was divided into 12 equal areas of interest (A01). In order to enhance the precision of determination of V̇a/Q̇, images were then condensed into a 32 x 32 matrix form in the computer memory, with each pixel or elementary unit of this matrix corresponding to a surface of approximately one square cm. Regional V̇a/Q̇ was computed in each pixel by dividing ventilation by perfusion counts and was consequently normalized to an overall value of 1.

A histogram of the distribution of the value of V̇a/Q̇ in each pixel was drawn and characteristic parameters (standard deviation and skewness) were computed.

In addition, V̇a/Q̇ ratios were computed in the 12 AO1 of each lung; this allowed regional comparisons between repeated examinations, since postural effects were minimal.

Table 1—Effects of Placebo (P) or Almitrine (A) on Blood Gas, Ventilation and Hemodynamics, Measured at Rest, during Control Period (Rc) without and after Drug (Ra or Rp)

<table>
<thead>
<tr>
<th>Laboratory Test*</th>
<th>Placebo</th>
<th>Almitrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ṙc (L/min)</td>
<td>261 ± 12</td>
<td>258 ± 16</td>
</tr>
<tr>
<td>Ṙp (L/min)</td>
<td>235 ± 20</td>
<td>238 ± 20</td>
</tr>
<tr>
<td>V̇O₂ (ml/min)</td>
<td>92 ± 0.2</td>
<td>92 ± 0.2</td>
</tr>
<tr>
<td>V̇CO₂ (ml/min)</td>
<td>95 ± 3.4</td>
<td>94.5 ± 2.6</td>
</tr>
<tr>
<td>Pp (mm Hg)</td>
<td>28 ± 2</td>
<td>27 ± 2</td>
</tr>
<tr>
<td>Pf (mm Hg)</td>
<td>9 ± 2</td>
<td>7 ± 2</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>5 ± 0.4</td>
<td>5 ± 0.4</td>
</tr>
<tr>
<td>CaO₂ - CVO₂ (mL/L)</td>
<td>55 ± 0.3</td>
<td>54 ± 0.3</td>
</tr>
<tr>
<td>P(V̇a/Q̇) (mm Hg)</td>
<td>35 ± 1.2</td>
<td>35.3 ± 1.8</td>
</tr>
<tr>
<td>V̇D/V̇T (%)</td>
<td>43 ± 3</td>
<td>43 ± 3</td>
</tr>
<tr>
<td>Q̇S/Q̇ (%)</td>
<td>26 ± 3</td>
<td>26 ± 3</td>
</tr>
<tr>
<td>PVR (mm Hg/L)</td>
<td>3.8 ± 0.3</td>
<td>4 ± 0.6</td>
</tr>
</tbody>
</table>

*Each value represents the mean ± SEM
†Rc-Rs significantly different from placebo values; p<0.05
‡Rc-Rs significantly different from placebo values; p<0.001
§to convert to millimole per liter, divide by 2.24
Definition of abbreviations: PaO₂, ṖO₂, PaCO₂=arterial, mixed venous, oxygen and carbon dioxide partial pressures, Ha = arterial hydrogen ion concentrations; A-AO₂, a-AO₂ = alveolar – arterial oxygen and carbon dioxide gradients.

f = breathing frequency; V̇E ≡ expired minute ventilation; V̇O₂ = oxygen uptake; R = respiratory exchange ratio; HR = heart rate; Ppa = mean pulmonary artery pressure; CO = cardiac output; CaO₂ – CVO₂ = arteriovenous differences in O₂ concentrations. V̇D/V̇T = ratio of physiologic dead space to tidal volume, Q̇S/Q̇ = the ratio of venous admixture to total blood flow; PVR = pulmonary vascular resistance.
**Results**

**Arterial Blood Gas, Ventilation and Hemodynamic Study at Rest (Table 1, Fig 1)**

For PaO\(_2\), there was an increase in every patient, mean +12.0±2.1 mm Hg (p<0.001) between Rc and Ra. For PaCO\(_2\), a decrease in every patient, mean -6.0±0.7 (p<0.001) observed with administration of almitrine compared to placebo (Rc - Rp).

Arterial oxygen saturation (SaO\(_2\)) and concentration of oxygen (CaO\(_2\)) significantly increased after administration of almitrine compared to placebo: respectively, for SaO\(_2\) from 89.0±1.2 to 94.0±1.1 percent with almitrine and 91.3±1.2 to 91.5±1.3 percent with placebo (p<0.001); for CaO\(_2\) from 198±11 to 207±10 mL\(\cdot\)L\(^{-1}\) with almitrine and from 202.70±5.1 to 203.4±5.7 mL\(\cdot\)L\(^{-1}\) with placebo (p<0.005).

There was no significant change in respiratory rate, minute ventilation and VO\(_2\) between almitrine and placebo.

Compared to placebo, almitrine induced a marked improvement in P\(\times\)aO\(_2\) (-10.0±1.9 mm Hg; p<0.001) and Pa-P\(\times\)CO\(_2\) (-3.5±2 mm Hg; p<0.05). Dead space and venous admixture decreased significantly with almitrine and remained constant with placebo. There was no correlation between the fall in PaCO\(_2\) after almitrine and the variations in VE expressed as a percentage of the initial value.

Cardiac output, CaO\(_2\)-CvO\(_2\), systemic hemodynamics and pulmonary vascular resistance did not change significantly after administration of almitrine compared to placebo. Almitrine induced a slight but significant increase in mean pulmonary artery pressure (PAP) (+4.0±1.5, p<0.05). It should be noted that, coincidentally, mean pulmonary artery pressure and pulmonary vascular resistance were already significantly greater in the almitrine group before treatment despite the strict randomization.

Plasma concentration of almitrine ranged from 34 to 311 ngr/ml and was not correlated with blood gas, ventilation and hemodynamic values. No significant side-effect was observed.

**Arterial Blood Gas, Ventilation and Hemodynamic Studies on Exercise (Table 2, Fig 1)**

For PaO\(_2\), there was a mean increase of +6.4±1.9
Table 2—Effects of Placebo (Ec) or Almitrine (EA) on Blood Gas Ventilation and Hemodynamics, Measured on exercise during Control Period (Ec) Without and after Drug (EA or EP)

<table>
<thead>
<tr>
<th>Laboratory Test*</th>
<th>Placebo</th>
<th>EP</th>
<th>Ec</th>
<th>Almitrine</th>
<th>EA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2 (mm Hg)</td>
<td>58.1±4.1</td>
<td>55.4±3.6</td>
<td>55.9±4.3</td>
<td>62.3±5.2†</td>
<td></td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td>47.5±1.7</td>
<td>47±2.3</td>
<td>50.6±2.7</td>
<td>44.3±3.1‡</td>
<td></td>
</tr>
<tr>
<td>Hb* (nmol/L)</td>
<td>45.2±1.8</td>
<td>44.1±1.5</td>
<td>44.1±3.3</td>
<td>41.6±1.4</td>
<td></td>
</tr>
<tr>
<td>(A-α)O2 (mm Hg)</td>
<td>41.4±3.2</td>
<td>43.9±3.8</td>
<td>44.8±3.7</td>
<td>43.5±3.8</td>
<td></td>
</tr>
<tr>
<td>(a-α)CO2 (mm Hg)</td>
<td>8±1.8</td>
<td>9.7±1.8</td>
<td>10.1±1.9</td>
<td>7±1.9†</td>
<td></td>
</tr>
<tr>
<td>Vd/Vt (%)</td>
<td>48±2.5</td>
<td>51±2</td>
<td>49.3±5</td>
<td>46.1±6†</td>
<td></td>
</tr>
<tr>
<td>Qs/Qt (%)</td>
<td>23.5±4.3</td>
<td>22.9±3.9</td>
<td>19.3±1.7</td>
<td>17.6±1.5</td>
<td></td>
</tr>
<tr>
<td>f (breaths/min)</td>
<td>27.1±1.6</td>
<td>26.9±2</td>
<td>25±1.8</td>
<td>26.6±1.8</td>
<td></td>
</tr>
<tr>
<td>Ve (L/min)</td>
<td>19.3±1.7</td>
<td>17.6±1.5</td>
<td>17±1.8</td>
<td>18.3±2†</td>
<td></td>
</tr>
<tr>
<td>VO2 (ml/min)</td>
<td>653.7±41.2</td>
<td>591.6±34.8</td>
<td>561.1±82.9</td>
<td>555.4±81.3</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>0.89±0.04</td>
<td>0.83±0.03</td>
<td>0.88±0.04</td>
<td>0.88±0.04</td>
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</tr>
<tr>
<td>HR (beats/min)</td>
<td>110.1±4.5</td>
<td>110.5±4.9</td>
<td>121±4.4</td>
<td>120.8±4.8</td>
<td></td>
</tr>
<tr>
<td>Ppa (mm Hg)</td>
<td>42.3±3.7</td>
<td>41.5±3.3</td>
<td>49.8±4</td>
<td>54.5±4.8</td>
<td></td>
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<tr>
<td>Pw (mm Hg)</td>
<td>12±2.7</td>
<td>12.4±2.1</td>
<td>13.8±2.6</td>
<td>15.3±2.4</td>
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<tr>
<td>CO (L/min)</td>
<td>8.1±0.8</td>
<td>7.25±0.4</td>
<td>7.04±1.1</td>
<td>7.17±1.2</td>
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</tr>
<tr>
<td>CaO2−CvO2 (ml/L)</td>
<td>8.2±0.7</td>
<td>8.81±0.4</td>
<td>9.91±1.1</td>
<td>9.89±1.1</td>
<td></td>
</tr>
<tr>
<td>PSO4 (mm Hg)</td>
<td>30.4±2.2</td>
<td>27.6±1.4</td>
<td>27.3±1.6</td>
<td>28.5±1.3†</td>
<td></td>
</tr>
<tr>
<td>PVR (mm Hg/L/min⁻)</td>
<td>3.82±0.3</td>
<td>4.1±0.4</td>
<td>6.46±1.4</td>
<td>7.06±1.47</td>
<td></td>
</tr>
</tbody>
</table>

*Each value represents the mean ± SEM
†Ec – EA significantly different from placebo values; p<0.05
‡Ec – EA significantly different from placebo values; p<0.001
§To convert to millimole per liter, divide by 2.24.
For definition of abbreviations see Table 1.

mm Hg (p<0.001) between Ec and EP, and for PaCO2 a mean decrease of −6.3±0.8 mm Hg (p<0.001) with almitrine compared to placebo (Ec − EP). The pattern of change in PaO2 and PaCO2 between rest and exercise was the same in both groups, with a slight fall in PaO2 and a rise in PaCO2. However, the higher PaO2 and lower PaCO2 with almitrine at rest persisted during exercise.

Compared to placebo, almitrine induced an improvement in a −αCO2 (−3.1±0.7 mm Hg; p<0.009); Vd/Vt (−3.2±1.2, percent p<0.005); Ve, (+1.3±0.6 L/min⁻¹ p<0.01); FvO2 (−1.2±0.6 mm Hg, p<0.04).

Although the increase in PAP with exercise is of borderline significance (+4.7±2 mm Hg, p = 0.063) changes in pulmonary arterial pressure and pulmonary vascular resistance were similar and nonsignificantly different between the two groups. The power of the statistical test can be estimated at 0.8. It would have been necessary to include 1.5 to 2 times more subjects in each group to prove with β equal to 10 percent.

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**Figure 2.** Distribution of local isotopic Vd/Vt ratios before and after almitrine (left) or placebo (right). Abcissa indicates distribution of Vd/Vt ratio. Ordinate represents the frequency of each value, expressed as percentage of the total. Dotted area indicates blocks which disappear after treatment; bars indicate blocks which appear after treatment.
(power = 0.9) that the 4.8 mm Hg increase in PAP was not significant. Individual results (Fig 1) showed that there was a large scattering of hemodynamic values within both placebo and almitrine groups, and changes between rest and exercise were also very different. Some clearly increased their PAP, others less so even without drug, during the control period. Trends in hemodynamics do not seem to be modified by administration of almitrine.

Isotopic Study

Histogram of $\dot{V}A/Q$ ratios (Fig 2): In the almitrine group, the percentage of $\dot{V}A/Q$ above 1.5 and below 0.5 decreased (8.3 to 3.3 percent and 4.1 to 1.6 percent); at the same time, the percentage of $\dot{V}A/Q$ between 0.5 and 1 and between 1 and 1.5 increased respectively from 47.8 to 48.7 and from 39 to 46.4 percent. Comparatively, in the placebo group, there were only slight changes in the $\dot{V}A/Q$ distribution.

Standard error of the $\dot{V}A/Q$ distribution decreased in the almitrine group from 0.31 to 0.22 and remained constant in the placebo group (0.29 - 0.28); the difference between the two groups was significant ($p<0.05$). Changes in the skewness of the $\dot{V}A/Q$ distribution curves were similar in the two groups.

Regional distribution of $\dot{V}A/Q$ ratios: In zones where the $\dot{V}A/Q$ ratio was less than 0.8, it increased significantly ($p<0.05$) from 0.64 to 0.77 in patients treated by almitrine, but not in those treated by placebo (0.73 to 0.75). Similarly, in zones with a $\dot{V}A/Q$ ratio greater than 1.2, it decreased significantly ($p<0.02$) from 1.43 to 1.24 in patients treated by almitrine, but not in those treated by placebo (1.41 to 1.38).

Blood gases and ventilatory measurements during the isotopic study: During the control isotopic period (Riso), without drugs, the control values for PaO$_2$ ($A = 66 \pm 3$, $P = 61 \pm 4$ mm Hg), PaCO$_2$ ($A = 46 \pm 2$, $P = 43 \pm 0.5$ mm Hg) and VE ($A = 8.3 \pm 0.7$, $P = 9.1 \pm 0.7$ L min$^{-1}$) did not differ significantly from controls of the blood gas, ventilation and hemodynamic study (Rc, Table 1). Between Riso and Riso, there was a significant mean increase in PaO$_2$ ($+10 \pm 3$ mm Hg; $p<0.001$) and decrease in PaCO$_2$ ($-5.2 \pm 0.9$ mm Hg; $p<0.05$) with almitrine compared to placebo (Riso - Riso).

Discussion

The main findings of this acute study are: that almitrine at rest (3 mg/kg) causes a rise in PaO$_2$ ($+12$ mm Hg) and a fall in PaCO$_2$ ($-6$ mm Hg) in a group of hypoxemic patients with chronic bronchitis, without a concomitant rise in external ventilation; that the improvement in arterial blood gases persisted during exercise, where a greater increase in ventilation was observed after almitrine than placebo; and that these effects were associated at rest with significant but slight changes in mean pulmonary artery pressure.

Similar changes in arterial blood gases have been found in all studies with almitrine using either an intravenous bolus (0.5 mg/kg), a 30-60 minute infusion with different doses from 0.25 to 1 mg/kg or oral tablets (1 to 6 mg/kg) or supplemented with O$_2$ (40 to 60 percent O$_2$). In studies where blood gas levels were measured sequentially, the increase in PaO$_2$ preceded the fall in PaCO$_2$ and the increase in external ventilation.

The effect on blood gases which we observed three hours after oral intake of almitrine has been shown by other investigations to persist for about four hours. The improvement in blood gases was maintained in chronic studies where almitrine was given for one to six months.

In most studies with IV or oral almitrine, the average values of external ventilation rose, but the increase was barely significant in some. In all published studies, the rise in VE at rest failed to occur in some individual cases, and in our group of patients, mean VE did not increase at rest. Individual values rose in three patients, fell in three and were almost unchanged in two. Whatever the reasons for the different behaviors of individual minute ventilation in resting patients, the fact remains that PaCO$_2$ rose in all subjects and PaCO$_2$, O$_2$ and CO$_2$ alveolar-arterial gradients fell in seven of eight cases. These data, together with the lack of change in cardiac output and PaO$_2$, strongly suggest that the improvement in pulmonary gas exchange with almitrine is not necessarily due to a rise in external ventilation, but could also involve a change in the $\dot{V}A/Q$ distribution. Confirmation was obtained by our isotopic study showing a narrowing of $\dot{V}A/Q$ distribution with a decrease both in high and low $\dot{V}A/Q$ zones. The lack of sensitivity of isotopic studies excludes a close comparison between results in gas exchange and isotopic data; however, the improvement in blood gases is consistent with the observed $\dot{V}A/Q$ changes. Other studies, using isotopic or multiple inert gas techniques, have shown a similar decrease in low $\dot{V}A/Q$ zones with almitrine.

The mechanism of $\dot{V}A/Q$ changes after almitrine remains to be elucidated, but may involve a redistribution of ventilation, perfusion or both. In this study, no data concerning these redistributions are available; however, the lack of measurable changes in ventilation and the increase in mean pulmonary arterial pressure suggests preferentially a perfusion redistribution.

These results, the first on exercise with almitrine, show that improvement in arterial blood gases at rest with almitrine is maintained on exercise. In addition, changes in pulmonary artery pressure between rest
and exercise were similar in the placebo and almitrine groups.

The increase in resting mean pulmonary artery pressure in our patients is similar to that observed in other studies using similar or greater doses.4,10 The mechanism of the increase in pulmonary artery pressure is poorly understood; a local effect of almitrine on the pulmonary vascular bed is unlikely, since in vitro studies on isolated lung lobes have shown only slight and inconstant pulmonary vasoconstrictor effects or even a reduction in hypoxic pulmonary vasoconstriction.28-30 A constrictor effect involving carotid chemoreceptors is another possible explanation. In any case, this increase in pulmonary pressure is too small to have clinical significance.

In conclusion, almitrine improves arterial blood gases without deleterious effects on the pulmonary circulation in patients with chronic respiratory insufficiency. This improvement is maintained on exercise. However, it will be necessary in long-term studies to assess in these patients the therapeutic value of the almitrine-induced improvement in arterial blood gases.

References
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