Almitrine Decreases the Distensibility of the Large Pulmonary Arteries in Man

Philippe Herve, M.D.,* Dominique Musset, M.D.,* Gérald Simonneau, M.D.;* Wiltz Wagner, Jr., Ph. D.;† and Pierre Duroux, M.D.*

Almitrine improves blood gas values in patients with COPD, primarily through better ventilation-perfusion matching. The improvement comes largely from a vasomotor effect of the drug. The vasomotor mechanism is unknown. We suspected that decreased distensibility of the large pulmonary arteries was one probable effect of the drug. If present, reduced distensibility would explain many of the hemodynamic alterations produced by almitrine. To test this idea, we measured the diameter of the right pulmonary artery during systole and diastole both before and after almitrine administration in nine patients who were undergoing pulmonary cineangiography. Our calculations of the distensibility of the right pulmonary artery showed that almitrine caused a 60 percent decrease. This significant alteration in the stiffness of the large pulmonary arteries can account for the rise in systolic pressure, a change that would be expected to redistribute pulmonary blood flow upwards and thereby improve ventilation-perfusion balance.

\[P_{pa} = \text{pulmonary arterial pressure}; TPVR = \text{total pulmonary vascular resistance}; Dmax = \text{maximum (systolic) diameter}; Dmin = \text{minimum (diastolic) diameter}; pH_{a} = \text{arterial negative logarithm of hydrogen ion activity}\]

A lmitrine improves arterial blood gas values in COPD.¹ In some patients this effect is obtained by improving respiratory drive,² yet in most, the ventilatory changes are insufficient to account for the beneficial effect.¹³⁻⁵ Several studies have shown that almitrine improved ventilation-perfusion matching in COPD.¹³⁻⁵ We suspected that the improvement of gas exchange was related to redistribution of perfusion rather than to ventilatory alterations. The vasomotor effect that causes the possible redistribution of pulmonary blood flow is poorly understood. In a previous study on COPD patients, we found that almitrine increased pulmonary arterial systolic pressure without changing diastolic pressure, stroke volume or pulmonary vascular resistance.⁶ This alteration could be explained by a decrease in vessel wall distensibility.¹⁰ Because increased systolic pressures have been associated with upward redistribution of pulmonary blood flow¹¹ and improved ventilation-perfusion matching,¹² it is possible that almitrine is acting in this same manner to improve arterial blood gas levels. Our overall working hypothesis is that almitrine → decreased arterial wall distensibility → increased pulmonary arterial systolic pressure → upward redistribution of pulmonary blood flow recruitment of gas exchange vessels → improvement of arterial blood gases. The ability of almitrine to stiffen the pulmonary arterial walls is an essential part of this hypothesis. We tested this idea by measuring the acute changes in the diameter-pressure relationship of the right pulmonary artery before and after almitrine administration in patients undergoing pulmonary cineangiography.

**Materials and Methods**

We studied nine patients who were undergoing pulmonary cineangiography as preoperative evaluation for localized peripheral masses found on a chest x-ray film. Patients with obstructive tumors in segmental or large airways or with tumor extension to pulmonary arteries were excluded. The age range was 32 to 65 years. All patients had normal blood gas levels and near normal FEV₁ and VC (Table 1). None of the patients was receiving medication at the time of the study. They were free of cardiac, hepatic and renal disease. Because almitrine has been used as a postthoracic surgery drug to improve blood gas levels,¹³ it was not considered unethical to administer the drug preoperatively to these patients. All patients gave their informed consent.

The patients were studied while in the supine position. A triple lumen, thermodilution Swan-Ganz catheter and an NIH multiple side hole catheter (8 French) were introduced into the basilic vein from the right and left antecubital fossa, respectively, and advanced under fluoroscopic control and pressure monitoring into the right pulmonary artery. Pressure was monitored by Statham P23 Db transducers and recorded with a Gould multichannel recorder. The dynamic response of the NIH catheter-transducer system was determined with a sine wave pressure generator (Sinetest, Mediprom, Paris). The ratio of the true pressure and the measured pressure was plotted against the sine wave frequency and found to be flat (±5 percent) up to 20 Hz. Zero reference for pressure was placed at the midaxillary line. Heart rate was determined from the continuously monitored ECG. Systolic, diastolic, and mean Ppa were recorded using the NIH catheter. Right atrial pressure was measured via the Swan-Ganz catheter. Systemic arterial pressure

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was measured by sphygmomanometry. Cardiac outputs were obtained by averaging three successive thermodilution determinations (CO computer 9510 A, Edwards Laboratories) and converted to CI (L/min/m²). Pulmonary pulse pressure, TPVR (Ppa / CI, mm Hg/ min/m²/L = IU), systemic vascular resistance (systemic arterial – right atrial pressures) / CI, mm Hg/min/m²/L = IU, stroke index (CI/heart rate, ml/m²) were derived from pressures and cardiac output measurements.

Right pulmonary artery diameters were measured using a cinefluoroscopic technique as previously described. Briefly, the patients were placed in the supine position on a fluoroscope (Multiplex, CGR, Paris) and a contrast medium (Ioxaglate) was injected through the NIH catheter by a pneumatic injector. To avoid increasing pulmonary arterial diameter by the injection pressure, the NIH catheter was withdrawn into the right atrium just before the injection. A total of 1.5 ml/kg was injected at a rate of 30 ml/s. The fluoroscopic image was filmed at 50 frames/s using 35-mm film. Then a metal sphere of 40 mm in diameter was placed at the level of the right pulmonary artery and filmed for calibration. The effect of injection of contrast media on Ppa was examined in every patient by recording pressure through the Swan-Ganz catheter. There was no detectable change in pressure within the first ten cardiac cycles after injection.

The film was examined using a Tagarno projector. Diameters were measured from single frames for the first three beats after injection at the midpoint between the bifurcation of the main pulmonary artery and the first bifurcation of the right pulmonary artery. From these measurements (usually 100 frames), average values for the Dmax and the Dmin were obtained. The actual diameters (in millimeters) of the right pulmonary artery were calculated using the calibration factor, determined from the ratio of the diameter of the sphere measured of the film projection over the actual diameter of the sphere. The following parameters of arterial distensibility were computed: percent change in diameter, \((D_{\text{max}} - D_{\text{min}}) \times 100 / D_{\text{min}}\); slope of the diameter-pressure relationship, \((D_{\text{max}} - D_{\text{min}}) / \text{pulmonary pulse pressure, mm/mm Hg; pressure strain elastic modulus, } E_p = \text{pulmonary pulse pressure} \times D_{\text{min}} / (D_{\text{max}} - D_{\text{min}}), \text{g/cm}^2\).

Each measurement was made after a 30-min period of intravenous infusion of almitrine solvent in 5 percent dextrose (control period) and after a 30-min period of continuous infusion of almitrine at a dosage of 16 µg/kg/min. The periods were not randomized since intravenous almitrine has a long half-life. At the time of the measurements, pressures and cardiac outputs were recorded first, followed within 2 to 3 min by the angiographic procedure. The patients were instructed to hold their breath at the end of expiration during diameter and pressure measurements. In two additional patients, we determined that hemodynamic and diameter measurements were unaffected by repetitive injections. In one other patient, we investigated whether the changes in distensibility of the right pulmonary artery observed with almitrine also occurred during a comparable increase of Ppa elicited passively, i.e., we recorded the diameter-pressure relationship before and after application of a mild lower body positive pressure using medical antishock trousers (Jobst, Toledo, OH).

Results are given as mean ± SEM. Control and almitrine values were compared using a paired t-test; p<0.05 was considered significant. Diameter-pressure coordinates for the whole group of patients were analyzed in each experimental condition by linear regression analysis (least-squares method). Diameter-pressure co-

**TABLE 1 - PHYSIOLOGIC CHARACTERISTICS OF THE PATIENTS**

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Sex</th>
<th>Body Surface, m²</th>
<th>FEV, % Predicted</th>
<th>VC, % Predicted</th>
<th>pHa</th>
<th>PaO₂, mm Hg</th>
<th>PaCO₂ mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>F</td>
<td>1.45</td>
<td>100</td>
<td>95</td>
<td>7.59</td>
<td>115</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>M</td>
<td>1.72</td>
<td>74</td>
<td>92</td>
<td>7.40</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>M</td>
<td>1.74</td>
<td>105</td>
<td>100</td>
<td>7.40</td>
<td>105</td>
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<tr>
<td>4</td>
<td>60</td>
<td>M</td>
<td>1.69</td>
<td>60</td>
<td>80</td>
<td>7.35</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>57</td>
<td>M</td>
<td>1.55</td>
<td>75</td>
<td>80</td>
<td>7.38</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>54</td>
<td>M</td>
<td>1.42</td>
<td>105</td>
<td>90</td>
<td>7.48</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>64</td>
<td>M</td>
<td>1.42</td>
<td>76</td>
<td>60</td>
<td>7.45</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>M</td>
<td>2.10</td>
<td>80</td>
<td>90</td>
<td>7.45</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>M</td>
<td>1.80</td>
<td>100</td>
<td>105</td>
<td>7.45</td>
<td>110</td>
</tr>
</tbody>
</table>

Mean ± SEM 49.4 ± 13.2 1.65 ± 0.22 86.1 ± 7.5 88 ± 13.3 7.45 ± 0.05 93.1 ± 5.5 33.5 ± 2.3
Table 2—Effect of Almitrine on Pulmonary Hemodynamics*

<table>
<thead>
<tr>
<th>Heart Rate, beats/min</th>
<th>CI, L/min/m²</th>
<th>Right Atrial Pressure, mm Hg</th>
<th>Systolic Ppa, mm Hg</th>
<th>Diastolic Ppa, mm Hg</th>
<th>Mean Ppa, mm Hg</th>
<th>TPVR, IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>C A</td>
<td>C A</td>
<td>C A</td>
<td>C A</td>
<td>C A</td>
<td>C A</td>
<td>C A</td>
</tr>
<tr>
<td>1 75/90</td>
<td>4.3±2.8</td>
<td>3.7±4.3</td>
<td>15.0±28.0</td>
<td>3.0±5.0</td>
<td>10.0±15.0</td>
<td>2.3±2.9</td>
</tr>
<tr>
<td>2 55/55</td>
<td>2.8±2.8</td>
<td>3.0±3.0</td>
<td>28.0±43.0</td>
<td>7.0±7.0</td>
<td>12.5±20.0</td>
<td>4.4±7.1</td>
</tr>
<tr>
<td>3 80/85</td>
<td>3.1±3.1</td>
<td>2.0±2.0</td>
<td>27.5±45.0</td>
<td>10.0±10.5</td>
<td>15.0±26.5</td>
<td>4.0±6.1</td>
</tr>
<tr>
<td>4 80/80</td>
<td>3.2±3.9</td>
<td>8.0±6.0</td>
<td>24.0±45.0</td>
<td>12.0±26.0</td>
<td>16.0±33.0</td>
<td>5±8.4</td>
</tr>
<tr>
<td>5 100/110</td>
<td>3.2±3.9</td>
<td>2.0±3.0</td>
<td>20.0±35.0</td>
<td>9.0±14.0</td>
<td>14.0±20.0</td>
<td>2.9±3.6</td>
</tr>
<tr>
<td>6 75/90</td>
<td>5.0±5.2</td>
<td>6.0±9.0</td>
<td>22.0±36.0</td>
<td>12.0±16.0</td>
<td>17.5±25.0</td>
<td>3.5±4.8</td>
</tr>
<tr>
<td>7 100/110</td>
<td>4.7±5.5</td>
<td>2.0±4.0</td>
<td>22.0±38.0</td>
<td>8.0±15.0</td>
<td>13.0±27.0</td>
<td>2.7±4.9</td>
</tr>
<tr>
<td>8 75/85</td>
<td>3.3±3.8</td>
<td>2.0±3.0</td>
<td>20.0±36.0</td>
<td>9.0±14.0</td>
<td>13.0±22.0</td>
<td>3.9±5.7</td>
</tr>
<tr>
<td>9 100/120</td>
<td>4.7±5.5</td>
<td>5.0±2.5</td>
<td>22.0±38.0</td>
<td>8.0±15.0</td>
<td>13.0±27.0</td>
<td>2.7±4.9</td>
</tr>
<tr>
<td>Mean±</td>
<td>82±92±3.9±4.4±3.5±4.0±23.2±22.8±14.7±7.1±3.9±5.8±</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>5±7</td>
<td>0.3±0.4</td>
<td>0.8±0.9</td>
<td>1.6±2.0</td>
<td>1.0±2.0</td>
<td>1.1±2.0</td>
</tr>
</tbody>
</table>

*p Values <0.01 <0.05 <0.001 <0.02 <0.01

*Control, C; almitrine, A.

 ordinates were considered to fit a linear relationship at a significance level of p<0.05. Diameter was considered to be the dependent variable and pressure the independent variable.

RESULTS

The hemodynamic data are shown in Table 2. With almitrine, systolic and diastolic Ppa increased by 15.5±2 mm Hg (p<0.001) and 4.5±2 mm Hg (p<0.01), respectively, causing a large increase in pulmonary pulse pressure (+78 percent). Mean Ppa increased by 9±2 mm Hg (p<0.01). Systemic arterial pressure and right atrial pressure did not change. Cardiac index increased by 13 percent (p<0.01). Stroke index did not change. There was a rise in TPVR (48 percent, p<0.05). Systemic vascular resistance did not change.

An example of the pulmonary angiograms recorded for measurement of Dmax and Dmin is shown in Figure 1. Both Dmax and Dmin increased with almitrine by 4 percent (p<0.05) and 7 percent (p<0.001), respectively (Table 3). However, the diameter difference (Dmax - Dmin) did not change significantly. A decrease in the distensibility of the pulmonary artery with almitrine is demonstrated by changes in all parameters of distensibility: mean percent change in diameter decreased by 25 percent (p<0.05),

![PA Diameter vs Ppa](image1)

FIGURE 2. Individual diameter (ordinate) vs pressure (abscissa) for relationships for the right pulmonary artery in control conditions (open circles, left panel) and with almitrine (solid circles, right panel). Each diameter-pressure relationship is plotted for each patient, using two points and assuming a linear diameter-pressure relationship within the cardiac cycle. The lower point corresponds to the minimum diameter and to the diastolic Ppa, the higher to the maximum diameter and to the systolic Ppa. There is a decrease in the slope of the diameter-pressure plot in every patient with almitrine, indicating a decrease in distensibility.
Table 3—Effect of Almitrine on Diameter and Distensibility of the Right Pulmonary Artery

<table>
<thead>
<tr>
<th>Dmin, mm</th>
<th>Dmax, mm</th>
<th>% D</th>
<th>ΔD/ΔP, mm/mm Hg</th>
<th>Ep, g/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>A</td>
<td>C</td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>23.0±0.6</td>
<td>24.6±0.8</td>
<td>26.8±0.8</td>
<td>27.8±0.8</td>
<td>16±2</td>
</tr>
</tbody>
</table>

p Values: C: Control; A: Almitrine; ΔD/ΔP: slope of the diameter-pressure relationship; Ep: pressure-strain elastic modulus.

The mean slope of the diameter-pressure plot decreased by 50 percent (p<0.01), and mean elastic modulus (Ep) increased by about 150 percent (p<0.001). The decrease in the slope of the diameter-pressure relationship was observed in every patient (Fig 2). The diameter-pressure coordinates were linearly correlated in both control and almitrine conditions (r = 0.75, p<0.01 and r = 0.60, p<0.01, respectively). In each experimental condition, the slope of the diameter-pressure relationship calculated for the whole group by regression analysis was not different from the mean of all individual slopes (0.13 and 0.28 by linear regression analysis vs 0.13 and 0.27 by arithmetic method).

Application of the lower body positive pressure resulted in an increase in systolic Ppa from 25 to 37 mm Hg and in diastolic Ppa from 8 to 18.5 mm Hg, in Dmax from 26.5 to 27.5 mm and in Dmin from 22 to 23 mm, values which are in the same range as the systolic and diastolic Ppa and diameter values measured during control and almitrine, respectively. The slope of diameter-pressure relationship decreased by 8 percent and the elastic modulus (Ep) increased by 9.5 percent, small changes compared with those that occurred after almitrine administration.

**DISCUSSION**

In this study, we tested the hypothesis that almitrine would reduce the distensibility of the large pulmonary arteries in intact man. To test this, we used cineangiographic analysis to measure the diameter of the right pulmonary artery. Combining the diameter measurement with pressure determinations from a high-frequency response system, we could calculate whether almitrine altered pulmonary arterial wall distensibility as reflected by the diameter-pressure relationship. All parameters of distensibility changed in a way that demonstrates a large decrease in the pulmonary arterial wall distensibility with almitrine.

We measured the diameter of the right pulmonary artery because its orientation is orthogonal to the x-ray beam in postero-anterior projections, thereby increasing the certainty of measuring the actual diameter. Once the diameter is measured during both systole and diastole, it is necessary to make certain assumptions about the diameter changes in order to calculate vessel distensibility. The first assumption is that the pulmonary artery is circular in cross section and remains as a circle throughout the study. This assumption permits us to measure a single diameter and relate that measurement to cross-sectional area. We assume further that the diameter-pressure relationships of the artery provide an accurate representation of its distensibility. This assumption is based on the idea that, in a general sense, elasticity determines the extent to which vessel expansion is resisted. Therefore the elastic properties of a vascular wall can be characterized if the transmural pressure and vessel dimensions can be measured during a cardiac pulsation. Since the Ppa and diameter are linearly related within a cardiac cycle, the degree of distensibility can be determined in a simple way by relating the amplitude of the diameter pulsation to the amplitude of the pressure pulsation.

Cineangiography was the most practical technique available to us to measure the right pulmonary arterial diameters in intact man. The accuracy of the diameter measurements depends on how well the vessel can be resolved. With the technique we used, resolution is attenuated by geometric distortion and blurring due to wall motion. The geometric attenuation (unsharpness, Uq) was calculated to be 0.02 mm using the relationship, Uq = F x b/(d - b), where F is the diameter of the focal spot (1 mm); b is the thickness of the object (approximately 20 mm); and d is the film-to-focus distance (1,000 mm). The blurring due to the
wall motion was minimized by measuring the diameters during midsystole and late diastole when the rate of change of pressure and diameter is least. Blurring was further reduced using a short exposure (5 ms/frame). Two separate studies\textsuperscript{14,15} showed that the minimum change in vessel diameter detectable with an angiographic technique similar to ours was approximately 0.2 mm. Since the absolute change we measured was approximately 1.5 mm, an accurate measurement was well within the range of our resolution capability. Further, the diameters were measured by two separate observers who were unaware of the treatment (control or almitrine). As an additional check of accuracy, we compared interobserver and intraobserver agreement. In 100 trials of randomly chosen vessels, the interobserver agreement was \( r = 0.88, \) \( p < 0.01, \) and the intraobserver agreement was \( r = 0.90, p < 0.01, \) indicating that the observers could reproduce their own measurements and that their measurements agreed well with each other. The observers agreed in every single case on the direction of change with almitrine. Finally, our elastic modulus (\( E_p \)) values for the right pulmonary artery in control conditions were not different from those measured by others, using either the same angiographic technique,\textsuperscript{15,31,32} or electrical strain-gauge calipers.\textsuperscript{17,19,20} In sum, these data permit us to have confidence about the accuracy of the measurements.

Our findings raise the question about the mechanism of distensibility change. Vessel distensibility can be acutely reduced by either smooth muscle contraction\textsuperscript{83} or the vessel distending sufficiently to reach the alinear part of its pressure-volume curve that precedes the plateau.\textsuperscript{10,22} If the stroke volume remained unchanged, decreased distensibility should increase the pulse pressure without changing the diastolic pressure.\textsuperscript{19} With almitrine, the stroke volume did not change and the pulse pressure increased. However diastolic pressure and pulmonary vascular resistance increased with almitrine, suggesting an increased vasomotor tone in the small muscular arteries in addition to the change in the large pulmonary arteries. Due to this increased downstream resistance, the minimum diameter of the right pulmonary artery increased, which indicated an increase in the diastolic volume of the large pulmonary arteries. Thus, pure passive distension of the large pulmonary arteries could have contributed to the decrease in pulmonary arterial distensibility. However, several investigations have demonstrated that large pulmonary arteries do not reach the alinear portion of their pressure-volume curve under pressures of about 45 mm Hg.\textsuperscript{17-19,21}\textsuperscript{4} In this study, all patients had systolic Ppa less than 45 mm Hg and the relationship between pulmonary artery diameters and pressure coordinates was linear in control and almitrine conditions. This suggests, therefore, that a decreased distensibility from the diameter-pressure plateau is not the predominant cause. This idea is further supported by the experiment in which we increased Ppa to 37 mm Hg with lower body positive pressure and found a small distensibility decrease compared with that found with almitrine. Moreover, in three of the nine patients the vessel Dmax values did not change even though there was a decrease in distensibility; vessel enlargement obviously did not figure in these cases. This accumulation of evidence leads us to believe that the decrease in pulmonary arterial distensibility observed with almitrine resulted predominantly from an increased vasomotor tone in the large pulmonary arteries.

This is the first study to investigate directly the effects of almitrine on pulmonary vascular distensibility. In two earlier studies of the hemodynamic effects of almitrine in man, an increase in Ppa without a change in pulmonary vascular resistance and stroke volume was observed.\textsuperscript{7-25} However, the systolic and the diastolic Ppas were not reported. In a recent study, we observed that almitrine increased pulmonary arterial pulse pressure without causing changes in diastolic Ppa, pulmonary vascular resistance or stroke volume in COPD patients.\textsuperscript{8} These data are all suggestive of a decrease in pulmonary arterial distensibility, but the actual demonstration of a decreased distensibility with almitrine has not been previously reported.

Some authors suggest that improvement in blood gas levels with almitrine is related to ventilatory changes.\textsuperscript{2} In most studies, however, based on both isotopic and multiple inert gas methods, the blood gas improvement appears to come from a diversion of the pulmonary blood flow, from areas of low ventilation-perfusion ratio to areas of normal or high ventilation-perfusion ratios.\textsuperscript{3,5,6} One study of COPD patients in the seated position showed upward redistribution of blood flow with almitrine with no change in ventilation, but with concomitant improvement in blood gas values.\textsuperscript{6} Blood flow is redistributed upwards when large pulmonary artery distensibility is decreased,\textsuperscript{11} an alteration that would redistribute blood flow from regions of low ventilation-perfusion ratio to areas of high ventilation-perfusion ratio and thereby improve blood gas levels. This redistribution of blood flow also could be partly due to effects on smaller muscular arteries in which almitrine has been shown to reinforce hypoxic vasoconstriction.\textsuperscript{36}

We combine the results in the literature with the findings of this study that almitrine decreases the distensibility of the large pulmonary arteries to form the following working hypothesis: almitrine decreased arterial wall distensibility and increased pulmonary vascular resistance \( \rightarrow \) redistribution of pulmonary blood flow \( \rightarrow \) recruitment of gas exchange vessels \( \rightarrow \) improvement of arterial blood gas levels.
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REFERENCES

9 Herve PH, Simonneau G, Duroux P. Almitrine decreases compliance of pulmonary arteries in COPD. Chest 1983; 94:1119-20