High-dose Almitrine Bimesylate Inhibits Hypoxic Pulmonary Vasoconstriction in Closed-chest Dogs
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The effect of almitrine bimesylate on the hypoxic pulmonary vasoconstrictor (HPV) response was studied in seven closed-chest dogs anesthetized with pentobarbital and paralyzed with pancuronium. The right lung was ventilated continuously with 100% O₂, while the left lung was ventilated with either 100% O₂ ("hyperoxia") or with an hypoxic gas mixture ("hypoxia"); end-tidal P'O₂ = 50.1 ± 0.1 mm Hg. Cardiac output (CO) was altered from a "normal" value of 3.10 ± 0.18 l·min⁻¹ to a "high" value of 3.92 ± 0.16 l·min⁻¹ by opening arteriovenous fistulae which allowed measurements of two points along a pressure-flow line. These four phases of left lung hypoxia or hyperoxia with normal and high cardiac output were repeated in the presence and absence of almitrine. Almitrine bimesylate was administered as a constant infusion of 14.3 µg·kg⁻¹·min⁻¹ for a mean plasma concentration of 219.5 ± 26.4 ng·mL⁻¹. Relative blood flow to each lung was measured with a differential CO₂ excretion (VCO₂) method corrected for the Haldane effect. With both lungs hyperoxic, the percent left lung blood flow (%QL/QL+QH) was 44 ± 1%. When the left lung was exposed to hypoxia, the %QL/QL+QH decreased significantly to 22 ± 1%. However, with the administration of almitrine, the %QL/QL+QH during left lung hypoxia increased significantly to 36 ± 2%. The arterial oxygen tension decreased significantly between hyperoxia (PaO₂ = 633 ± 6 mm Hg) and hypoxia (271 ± 51 mm Hg). With the addition of almitrine, there was no change during hyperoxia; however, during hypoxia, the PaO₂ decreased significantly to 124 ± 15 mm Hg. Cardiac output did not influence these findings. The pulmonary vascular conductance (G) is the slope of the pressure-flow line. The pulmonary vascular conductance of the right lung (G₂) decreased significantly to 1.0 ± 0.1 dyne·cm⁻¹·cm²·s⁻¹ during both hyperoxia and hypoxia. The same was true at normal and high cardiac output. The pulmonary vascular conductance of the left lung (G₁) decreased significantly between hyperoxia (1.24 ± 0.1 dyne·cm⁻¹·cm²·s⁻¹) and hypoxia (0.7 ± 0.1 dyne·cm⁻¹·cm²·s⁻¹). However, with the addition of almitrine, G₁ decreased significantly during hypoxia (0.8 ± 0.1 dyne·cm⁻¹·cm²·s⁻¹), but not during hypoxia (0.8 ± 0.1 dyne·cm⁻¹·cm²·s⁻¹). The same was true at normal and high cardiac output. It is concluded that almitrine bimesylate caused non-specific pulmonary vasoconstriction that was greater in the 100% O₂ ventilated lung than in the hypoxic lung regions. Therefore, blood flow was diverted from the hypoxic back to the hypoxic lung causing a reduction of the HPV response. (Key words: Almitrine bimesylate. Hypoxia: pulmonary vascular response. Lung blood flow: hypoxic pulmonary vasoconstriction; shunting; vascular conductance. Oxygen: blood levels.)

ALMITRINE BIMESYLATE stimulates peripheral chemoreceptors,¹,² thus increasing ventilatory response to hypoxia.³⁻⁵ However, interest in the pulmonary vasomotor effects of almitrine bimesylate has been stimulated by the observation that, in patients with chronic obstructive pulmonary disease, the improvement in pulmonary gas exchange following this drug may not be wholly explained by the increases in minute ventilation (Vₐ) which nearly always occur.⁶⁻¹⁴ Based on indirect evidence, investigators have both proposed⁶⁻¹⁴ and denied⁶⁻¹⁴ that enhancement of hypoxic pulmonary vasoconstriction (HPV) by almitrine bimesylate is a possible mechanism for this improvement in gas exchange. The present study examined this controversy and tested the effect of almitrine bimesylate on hypoxic pulmonary vasoconstriction.

Methods
ANESTHESIA AND SURGERY
Seven female dogs of mixed breed with mean weight of 22.2 ± 0.6 kg were anesthetized with a bolus of 30 mg·kg⁻¹ intravenous pentobarbital followed by an infusion at 0.81–4.08 mg/min (Harvard® Infusion Pump model #902). The trachea was intubated initially with a 10-mm cuffed endotracheal tube, and mechanical ventilation was begun. Muscle paralysis was established with 0.05 mg·kg⁻¹ intravenous pancuronium supplemented with 0.2–0.5 mg·min⁻¹.

After subcricoid tracheostomy, a double-lumen Kottmeier® endobronchial tube (Rüscher Inc.) was placed. Complete lung isolation was verified by auscultation and the demonstration that cross-contamination did not occur when the left lung was ventilated with an hypoxic gas mixture. A percent venous admixture of less than 5% during 100% O₂ ventilation was used to confirm
normal lung function and, particularly, that the right upper lobe bronchus was not obstructed by the double-lumen tube. The lungs were ventilated synchronously with 100% O₂ via a Harvard dual-piston respirator with 5 cm H₂O of PEEP applied by water seal. Tidal volumes were selected to produce equal driving pressures, i.e., equal peak airway pressures of 15–20 cm H₂O. Inspired CO₂ and/or the respiratory rate were adjusted to keep right and left end-tidal P CO₂ close to 35–40 mmHg. Each piston of the Harvard ventilator was part of a separate gas circuit, with its gas composition determined by separate flow meters. Right and left lung inspired, end-tidal, and mixed expired P CO₂ and P O₂ were measured by a mass spectrometer (Perkin-Elmer model #1100 Medical Gas Analyser), which was calibrated daily with gases of known composition and corrected for barometric pressure, temperature, and water vapor.

Peripheral veins were cannulated for intravenous fluid administration to maintain euvolesemia (285 ± 26 ml·h⁻¹ Normosol and/or 0.9% saline) and for infusion of almitrine bisninesylate. Almitrine was administered at a constant infusion of 14.3 μg·kg⁻¹·min⁻¹ (Harvard Infusion Pump model #600-910/290). Body temperature, measured by an esophageal temperature probe, was maintained at 38 ± 0.2°C with heating lamps, pads, and heated humidifier. Sodium bicarbonate (NaHCO₃) was available to correct metabolic acidosis. Urine was collected from a Foley catheter.

Arterial pressure (via femoral artery) and central venous pressure (via an external jugular vein) were measured. Pulmonary arterial and pulmonary arterial occlusion pressures (via femoral vein) were measured with a flow-directed Swan-Ganz catheter (American Edwards #95A-131H-7F). Pressures were measured continuously on an 8-channel Grass polygraph (Model #7WGI6PA Serial #791W3). The transducers (Statham model #P23BB and Gould-Statham model P23Db) were zeroed at the mid-cardiac level and calibrated to mmHg or cm H₂O, as appropriate. Thermocardiograms (Edwards cardiac output computer model #9510-A) were obtained in triplicate using an injection of 5 ml of ice-cold 5% dextrose in water.

Since the dual responses of HPV are flow diversion and a change in pulmonary artery pressure (PAP), two points were collected using normal and high cardiac outputs to generate the pressure-flow line. For the manipulation of cardiac output, two arteriovenous (AV) fistulae (4 mm 1D arterial end, 6 mm 1D venous end) were constructed, one between a femoral artery and vein, and the other between an internal carotid artery and external jugular vein. The cardiac output was “normal” when the shunts were closed and “high” when the shunts were open. The dog was anticoagu- lated with approximately 300 units·kg⁻¹ of heparin iv, followed by 50 units·kg⁻¹ every 30 min.

Relative blood flow to each lung was measured with a differential carbon dioxide elimination (VCO₂) method. For each lung, the expired gas was directed through a turbine spirometer with a digital electronic output (Boehringer Labs #8830) and a capnometer (Puritan-Bennett Corporation, Datex #CD-102-27-00), linked through an interface (Boehringer Labs #9040C) to a small digital computer (Commodore #4018). Carbon dioxide (CO₂) production was calculated continuously from the expired volume signals and from the difference between the inspired and mixed-expired CO₂ concentration. The excretion was corrected for the Haldane effect when one lung was ventilated with a hypoxic gas mixture. The left lung blood flow (Ql·VCO₂) was calculated as the product of the relative CO₂ excretion and the total cardiac output, as determined by thermodilution.

**STUDY DESIGN**

Prior to the experimental sequence, three 15-min trials of hypoxic (approximately 4% O₂, 5% CO₂, bal N₂) ventilation to the left lung were alternated with 100% O₂ ventilation to determine the presence of stable reproducible pulmonary blood flow and pressure responses to hypoxia. The study was divided into halves with a 90-min waiting period between the no almitrine/almitrine periods. Each half consisted of four phases, with the left lung either hyperoxic or hypoxic, and with the cardiac output either normal or high (table 1). To obtain steady-state conditions and to make measurements required approximately 30–40 min for each phase. Whether the almitrine or no-almitrine period was examined first was randomized, as were each of the four phases within each group.

The right lung was ventilated continuously with 100% O₂, while the left lung was ventilated either with 100% O₂ (hyperoxia) or with an hypoxic gas mixture (hypoxia). With a flow meter (Mathes model #7481T
series R7400) to control inspired O₂, CO₂, and N₂, the
left lung end-tidal PₐO₂ during hypoxia was maintained
at 50 mmHg; this was chosen to yield an oxygen tension
at the sensor site for HPV (PₐSO₂) that would be approxi-
mately a half maximal hypoxic stimulus.¹⁹

Almitrine bisimetholate was dissolved in its solvent,
malic acid, and diluted with 0.9% saline solution. It
was administered as a constant infusion of 14.3
µg·kg⁻¹·min⁻¹.

MEASUREMENTS

At each phase, the following measurements were made:
peak and mean airway (Pₐw) pulmonary (PAP)
and systemic arterial (SAP), central venous (CVP), and
pulmonary artery occlusion pressures (PAOP); total
cardiac output (CO) by thermodilution in triplicate;
body temperature (temp); inspired, end-tidal, and
mixed expired O₂ and CO₂ of each lung by mass spec-
trometer. Arterial and mixed venous blood gas samples
were collected to determine pH, PₐO₂, PₐCO₂ (Corning®
PH/Blood Gas Analyzer model #168); and hemoglobin
concentration (Sigma® Kit #525). At each experimental
condition, blood was also collected for analysis of
plasma almitrine concentration by high-performance
liquid chromatography (Perkin-Elmer® Liquid Chromat-
ography Series #10; Perkin-Elmer® LC-93 UV/Vis-
ible Spectrophotometer Detector).²⁰ Right and left tidal
volume (TV), respiratory rate (RR), and minute venti-
lation (Vₑ) were recorded.

CALCULATIONS

From the recorded data, blood flow, vascular con-
ductance, and the percent blood flow to the left lung
were calculated.

Pulmonary perfusion pressure (PPP) in mmHg was
calculated as mean PAP minus mean PAOP. Left
and right pulmonary vascular conductances (dyn⁻¹
·cm⁵·s⁻¹) were calculated from the respective lung
blood flow in 1·min⁻¹ divided by the perfusion pres-
sure in mmHg (X80).

Alveolar oxygen tension (PₐO₂) for the right lung
ventilated with 100% O₂ was calculated from the baro-
metric pressure minus the saturated water vapor pres-
sure minus the PₐCO₂. During hypoxic ventilation, the
addition of CO₂ to the inspired gas was sufficient to
introduce errors into the alveolar gas mixing equa-
tion.²¹ Therefore, left lung PₐO₂ was calculated as
the mean of the measured mixed expired PₐO₂ and the
mixed venous PₐO₂. End-capillary oxygen tension was
assumed to be equal to the calculated alveolar oxygen
tension. The oxygen contents of end-capillary, arterial,
and mixed venous blood were then calculated from:

\[ CO₂ = (1.34 \times Hb \times \% Sat) + (PₐO₂ \times 0.0031) \]

Per cent saturation (% Sat), corrected for pH and tem-
perature, was calculated from a nomogram for canine
hemoglobin.²²

Calculation of left lung blood flow was made by
two methods. The first method, based on differential
CO₂ excretion of each lung, was described above as
%Qₑ·Vₑ·CO₂. The second method for estimation of left
lung blood flow during the hypoxic periods (%Qₑ·Vₑ·CO₂)
was based on a variation of the traditional shunt equa-
tion which allowed for the difference between alveolar
oxygen tension of the hypoxic versus hyperoxic lung.²³,²⁴ This
equation assumed: 1) that the total anatomic
shunt flow (Qₛ/Qₑ) measured during 100% O₂
ventilation remained unchanged during hypoxic venti-
lation for corresponding experimental conditions;
and 2) that the apportionment of anatomic shunt flow,
whether to the right lung or the left lung, also
remained unchanged during hypoxic ventilation. The
errors associated with these assumptions regarding the
anatomic shunt flow during 100% O₂ ventilation were
small compared to the variations in left lung flow
during the experimental conditions. The stimulus for
HPV, the PₐSO₂,²⁵ was calculated from:

\[ PₐSO₂ = (PₐO₂)_{0.32} \times (PₐO₂)_{0.68} \]

STATISTICS

The data regarding general hemodynamic conditions
were analyzed by a one-way within-subjects analysis of
variance (ANOVA) for repeated measurements with
Neuman-Keuls test for specific differences. The data
involving hypoxic pulmonary vasoconstriction re-
ponses were analyzed by a three-way ANOVA for
repeated measures/randomized blocks, with the three
factors being gas mixture (hyperoxia/hypoxia), cardiac
output (normal/high), and drug (absence/presence). A
value of P < 0.05 was considered significant. Results
are expressed as mean ± standard error.

RESULTS

Since the general experimental conditions for pHa,
PₐCO₂, temperature, hemoglobin (Hb), SAP, CVP, air-
way pressure right lung (PₐawR), airway pressure left lung
(PₐawL), minute ventilation right lung (VₑR), and minute
ventilation left lung (VₑL) did not change significantly
between the eight phases of the study, only the control
measurements made during the 100% O₂-normal car-
diac output-no almitrine phase are presented in table 2.
The mean heart rate (HR) during the 100% O₂-normal
cardiac output state was 184 ± 10 bpm, and varied
between 179 ± 9 bpm to 206 ± 12 bpm. The mean
systemic vascular resistance (SVR) decreased signifi-
cantly for each normal/high cardiac output pair (3774
± 284 to 2872 ± 131 dyn cm⁻² s⁻¹), but otherwise was not affected by gas mixture or almitrine administration.

The results from each phase for the following variables are presented in Table 3. The normal and high cardiac outputs were significantly different from each other; however, neither the gas mixture or almitrine administration affected cardiac output. During hypoxia, the arterial oxygen tension (\(\text{Pa}_O_2\)) decreased in the presence of almitrine at both levels of cardiac output. Mixed venous oxygen tension (\(\text{PvO}_2\)) increased significantly between normal/high output pair, but was not affected by almitrine. During hypoxia, the alveolar \(\text{Pa}_O_2\) were not significantly different. During hypoxia, the \(\text{P}_{SO_2}\) the stimulus for HPV, increased significantly when the cardiac output increased; however, at each cardiac output level, the \(\text{P}_{SO_2}\) decreased significantly when almitrine was given.

The plasma concentration of almitrine bisemisolate was significantly different between the phases where it was infused or not infused. For the “no almitrine” control phases, very low concentrations were detected if almitrine had been infused during the first half of the study; and zero concentrations were detected when the

| Table 2. General Hemodynamic and Blood Gas Values during the 100% O₂-Normal Cardiac Output-No Almitrine Condition (n = 7, Mean ± SE) |
|-----------------|-----------------|-----------------|-----------------|
| \(\text{pH}_a\)  | 7.353 ± 0.009   | 7.353 ± 0.009   | 7.353 ± 0.009   |
| \(\text{Paco}_2\) (mmHg) | 39.2 ± 0.6 | 39.2 ± 0.6 | 39.2 ± 0.6 |
| temp (°C) | 38.0 ± 0.2 | 38.0 ± 0.2 | 38.0 ± 0.2 |
| Hb (g dl⁻¹) | 12.8 ± 0.3 | 12.8 ± 0.3 | 12.8 ± 0.3 |
| \(\text{SAP}\) (mmHg) | 147.9 ± 3.7 | 147.9 ± 3.7 | 147.9 ± 3.7 |
| \(\text{CVP}\) (mmHg) | 5.0 ± 0.5 | 5.0 ± 0.5 | 5.0 ± 0.5 |
| \(\text{Fw}\) (cm H₂O) | 11.2 ± 0.2 | 11.2 ± 0.2 | 11.2 ± 0.2 |
| \(\text{Fv}\) (cm H₂O) | 11.0 ± 0.2 | 11.0 ± 0.2 | 11.0 ± 0.2 |
| \(\text{TV}_1\) (ml min⁻¹) | 218 ± 2 | 218 ± 2 | 218 ± 2 |
| \(\text{TV}_2\) (ml min⁻¹) | 292 ± 2 | 292 ± 2 | 292 ± 2 |
| \(\text{V}_{ER}\) (ml min⁻¹) | 3599 ± 102 | 3599 ± 102 | 3599 ± 102 |
| \(\text{V}_{EX}\) (ml min⁻¹) | 3700 ± 226 | 3700 ± 226 | 3700 ± 226 |

\(\text{pH}_a\) = arterial pH; \(\text{Paco}_2\) = arterial carbon dioxide tension; temp = temperature; Hb = hemoglobin; \(\text{SAP}\) = mean systemic arterial pressure; CVP = mean central venous pressure; \(\text{P}_{awr}\) = mean airway pressure right lung; \(\text{P}_{awl}\) = mean airway pressure left lung; \(\text{TV}_1\) = tidal volume right lung; \(\text{TV}_2\) = tidal volume left lung; \(\text{V}_{ER}\) = minute ventilation right lung; \(\text{V}_{EX}\) = minute ventilation left lung.

The results from each phase for the following variables are presented in Table 3. The normal and high cardiac outputs were significantly different from each other; however, neither the gas mixture or almitrine administration affected cardiac output. During hypoxia, the arterial oxygen tension (\(\text{Pa}_O_2\)) decreased in the presence of almitrine at both levels of cardiac output. Mixed venous oxygen tension (\(\text{PvO}_2\)) increased significantly between normal/high output pair, but was not affected by almitrine. During hypoxia, the alveolar \(\text{Pa}_O_2\) were not significantly different. During hypoxia, the \(\text{P}_{SO_2}\) the stimulus for HPV, increased significantly when the cardiac output increased; however, at each cardiac output level, the \(\text{P}_{SO_2}\) decreased significantly when almitrine was given.

The plasma concentration of almitrine bisemisolate was significantly different between the phases where it was infused or not infused. For the “no almitrine” control phases, very low concentrations were detected if almitrine had been infused during the first half of the study; and zero concentrations were detected when the

almitrine infusion was randomized to the second half of the study (table 3).

During both hypoxia and hypoxia, pulmonary artery pressures were not increased significantly with in-

| Table 3. Effects of Almitrine on Various Hemodynamic and Blood Gas Parameters during Left Lung 100% O₂/hypoxia and Normal (NI)/high (HI) Cardiac Outputs (n = 7, Mean ± standard error) |
|-----------------|-----------------|-----------------|-----------------|
| \(\text{CO}\) (l/min) | 3.10 | 3.92 | 3.58 | 3.10 | 3.98 | 3.09 | 3.95 |
| \(\text{Pa}_O_2\) (mmHg) | 633 | 637 | 624 | 271 | 260 | 124 | 139 |
| \(\text{PvO}_2\) (mmHg) | 6 | 4 | 5 | 31 | 29 | 15 | 9 |
| \(\text{Pa}_O_2\) (mmHg) | 69 | 79 | 79 | 61 | 67 | 61 | 61 |
| \(\text{P}_{SO_2}\) (mmHg) | 1 | 1 | 3 | 2 | 2 | 1 | 1 |
| \(\text{P}_{awr}\) (mmHg) | 50 | 51 | 50 | 1 | 1 | 1 | 1 |
| \(\text{P}_{awl}\) (mmHg) | 54 | 57 | 51 | 1 | 1 | 1 | 1 |
| \(\text{P}_{awr}\) (mmHg) | 21 | 23 | 28 | 24 | 28 | 31 | 33 |
| \(\text{PAO}_2\) (mmHg) | 1 | 1 | 2 | 1 | 1 | 2 | 2 |
| \(\text{GA}\) (10⁻³ cm⁻¹ cm⁻³ s⁻¹) | 1.8 | 1.9 | 1.0 | 1.8 | 1.9 | 1.0 | 1.3 |
| \(\text{GL}\) (10⁻³ cm⁻¹ cm⁻³ s⁻¹) | 0.2 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| \(\%\text{VA}\) | 2.7 | 2.7 | 3.7 | 2.7 | 2.7 | 3.7 | 2.7 |
| \(\%\text{QL}_{V_{A}}\) | 0.6 | 0.3 | 0.6 | 0.6 | 0.3 | 0.6 | 0.6 |

* Indicates a significant difference between no almitrine/almitrine values (P < 0.05).

† Indicates a significant difference between normal/high cardiac output values (P < 0.05).
Since the dual responses of HPV are a change in pulmonary artery pressure and diversion of blood flow from the hypoxic lung, the data are presented as pressure-flow lines. The blood flow for each lung under each experimental condition is related to the 100% O\textsubscript{2} ventilation-normal cardiac output-no almitrine control phase to facilitate comparison, analysis, and discussion of the right versus left lung data.

For the right lung (fig. 1), which was always ventilated with 100% oxygen, the addition of almitrine caused vasoconstriction regardless of whether the left lung was being exposed to 100% O\textsubscript{2} or hypoxia. For the left lung (fig. 2), almitrine caused vasoconstriction when it was hyperoxic; however, when the left lung was hypoxic and HPV had occurred, no further constriction of the lung could be detected when almitrine was added. These data are further evaluated in figures 3 and 4.

**Fig. 1.** Pressure-flow relationship for the right lung. The blood flow to the right lung was calculated relative to the 100% O\textsubscript{2}-normal cardiac output-no almitrine phase. Compared to the control state when almitrine was absent (circles), the addition of almitrine (triangles) caused vasoconstriction in the right lung, which was represented by a slight shift of the points to the right. The right lung was always ventilated with 100% O\textsubscript{2}, and this vasoconstriction occurred both during left lung hyperoxia (open symbols) and hypoxia (filled symbols). For each pressure-flow line, the lower symbol represents the normal cardiac output phase and the upper symbol the high cardiac output phase.

Increases in cardiac output; however, they were increased significantly by the addition of almitrine. During both hyperoxia and hypoxia, the PAOP were not significantly different in the absence or presence of almitrine; however, there were some statistically significant increases between the hyperoxia-normal cardiac output phases with and without almitrine (7 ± 1 mmHg) versus the hypoxia-normal cardiac output and hypoxia-high cardiac output groups with almitrine (9 ± 1 mmHg).

There was no change in percent venous admixture (%VA) during 100% O\textsubscript{2} ventilation. The percent left lung blood flow (%Q\textsubscript{L,VA}) during hypoxia increased with the administration of almitrine.

Percent left lung blood flow (%Q\textsubscript{L,VA}) decreased significantly between 100% O\textsubscript{2} ventilation and hypoxia. During hypoxia, almitrine administration caused a significant increase in %Q\textsubscript{L,VA}.

**Fig. 2.** Pressure-flow relationship for the left lung. The blood flow to the left lung was calculated relative to the 100% O\textsubscript{2}-normal cardiac output-no almitrine phase. In the absence of almitrine (circles), active HPV was represented by a rightward and downward shift of the points from hyperoxia (open circles) to hypoxia (filled circles). With the addition of almitrine (triangles), there was constriction of the hypoxic left lung (open triangles); however, during hypoxia (filled triangles), no further constriction of the left lung was detected. For each pressure-flow line, the lower symbol represents the normal cardiac output phase and the upper symbol the high cardiac output phase.
Pulmonary vascular conductance is the reciprocal of pulmonary vascular resistance and is the slope of the pressure-flow line. The pulmonary vascular conductance of the right lung (G_R) was not affected by the type of gas mixture administered to the left lung (hyperoxia/hypoxia), but with the administration of almitrine, G_R was significantly decreased. The pulmonary vascular conductance of the left lung (G_L) decreased significantly between hyperoxia and hypoxia in the absence of almitrine. With the addition of almitrine, during hyperoxia, the G_L decreased significantly; and, during hypoxia, the G_L remained unchanged. During 100% O_2 ventilation (Fig. 3), both the right and left lungs were constricted in a similar manner by almitrine; therefore, the ratio of the conductances of the right lung/left lung (G_R/G_L) at each plasma almitrine level was a horizontal line with a slope not significantly different from zero (P > 0.4; R = −0.15). The ratio of conductances of the right lung/left lung was slightly greater than one because the right lung was larger than the left lung. In contrast, during left lung hypoxia (Fig. 4), the right lung was constricted by almitrine, whereas the left lung, already constricted by HPV, was not further constricted by almitrine. Therefore, the ratio of conductances of the right lung/left lung (G_R/G_L) was large at lower concentrations and small at higher almitrine concentrations (P < 0.004; R = −0.55).

![Diagram](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931383/)

**Fig. 4.** Effect of almitrine concentration on the ratio of pulmonary vascular conductances of the right lung/left lung (G_R/G_L) during hypoxia. The pulmonary vascular conductance of the right lung (G_R) which was hyperoxic during left lung hypoxia diminished with the addition of almitrine. The left lung which was constricted by HPV showed no further change in pulmonary vascular conductance (G_L) with addition of almitrine, so that the ratio of pulmonary vascular conductance of the right lung/left lung (G_R/G_L) became smaller with the addition of almitrine. Normal cardiac output-no almitrine (open circle); normal cardiac output-almitrine (filled circle); high cardiac output-no almitrine (open square); high cardiac output-almitrine (filled square).

**Discussion**

This study describes the effect of almitrine on the right and left lungs during conditions of 100% O_2 ventilation and regional hypoxia. Almitrine caused greater vasoconstriction in the lung ventilated with 100% O_2 than in lung regions already constricted by hypoxia. These results differed from a previous study from this laboratory which utilized a similar study design, but a smaller dose of almitrine. In that study, the left lung end-tidal oxygen tension (P_{ETO_2}) during hypoxia was 29.0 ± 0.5 mmHg and the almitrine infusion was 3.3 μg·kg⁻¹·min⁻¹. This dose was the same as that used by Romalde et al., who suggested that almitrine enhanced HPV. In our study, almitrine administered at this rate yielded a final plasma concentration of 52.9 ± 4.4 ng·ml⁻¹ and had no consistent effect on the HPV response or on the pulmonary vascular conductance of
Fig. 5. Predicted versus observed outcome for the effect of almitrine. If almitrine had enhanced HPV, as predicted, and had had no effect on the hypoxic lung, 1) the pulmonary vascular conductance of the hypoxic right lung (G_R) would have remained unchanged; 2) the pulmonary vascular conductance of the hypoxic left lung (G_L) would have decreased with enhancement of HPV; 3) so that the ratio of conductances of the right lung/ left lung (G_R/G_L) would have had a positive slope. However, the results showed that, with the administration of almitrine, 1) the pulmonary vascular conductance of the right lung (G_R) decreased due to non-specific vasoconstriction of the hypoxic right lung; 2) the pulmonary vascular conductance of the left lung (G_L) remained unchanged since it was already constricted by hypoxia; 3) so that the ratio of conductances of the right lung/ left lung (G_R/G_L) had a negative slope.

Pulmonary vascular conductance (G) is the slope of the pressure-flow line which allows presentation of flow diversion and PAP changes on the same graph. In figure 5, the predicted versus the observed outcome for the effect of almitrine are contrasted. If almitrine had had no effect on the hypoxic lung and had enhanced HPV, then the pulmonary vascular conductance of the right lung (G_R) would have remained unchanged, and the pulmonary vascular conductance of the left lung (G_L) would have decreased, so that the ratio of conductances of the right lung/ left lung (G_R/G_L) would have had a positive slope. However, the results showed that, with almitrine administration, G_R decreased and G_L remained unchanged, so that G_R/G_L had a negative slope (fig. 4). This suggested that the hypoxic right lung was constricted by almitrine, while the left lung which was already constricted by hypoxia was not constricted further by almitrine.

The stimulus for HPV (P_{SO2}), which is the oxygen tension at the sensor for HPV, is related to both the alveolar oxygen tension (P_{A02}) and the mixed venous oxygen tension (P_{V02}). Although the P_{A02} was held constant during hypoxia, the P_{V02} and P_{A02} decreased significantly with the administration of almitrine. Consequently, the P_{SO2} also decreased significantly with the administration of almitrine; this should have resulted in an increase in HPV. Instead, a decrease in flow diversion from the hypoxic left lung was observed due to vasoconstriction in the hypoxic right lung.

Several investigators have reported on almitrine and hypoxia. These studies may be divided into three groups: 1) normal and diseased humans; 2) preparations employing global hypoxia in vivo and in vitro; and 3) preparations employing regional hypoxia both in vivo and in vitro.

From studies of almitrine in healthy humans, patients with stable chronic obstructive pulmonary disease, and patients with respiratory failure, several investigators have reported variable changes in PAP, PVR, P_{A02}, and %VA, and V_e (table 4). Although these changes have occasionally been interpreted as enhancement of HPV, this was speculative and not supported by any direct attempt to quantitate either flow diversion or change in PAP which constitute the dual responses of HPV. Since many of these variables were not controlled or always measured, it is difficult to identify whether observed changes in PAP and PVR might be attributable to the action of almitrine as a nonspecific pulmonary vasoconstrictor; or whether the increase in P_{A02} and reduction of %VA might have been related to increases in cardiac output increasing P_{V02} or to improved perfusion to areas with an increased alveolar ventilation (V_a).

The concept that HPV was enhanced by almitrine is not sustained by the data available in the papers assembled. Of the experimental animal models, whole body hy-
Table 4. Evidence Interpreted as HPV Enhancement

<table>
<thead>
<tr>
<th>Species</th>
<th>Condition</th>
<th>Result*</th>
<th>Reference</th>
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<tbody>
<tr>
<td>1. Humans</td>
<td>Healthy</td>
<td>$\dot{V}_A/Q_c$</td>
<td>Guillerm, 1974$^{27}$</td>
</tr>
<tr>
<td>2. Humans</td>
<td>COPD</td>
<td>$\dot{Q}_A/Q_T$</td>
<td>Powles, 1983$^{3}$</td>
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<td></td>
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<td>$\dot{V}_A/Q_c$</td>
<td>Neukirch, 1974$^{28}$</td>
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<td>$\dot{V}_A/Q_c$</td>
<td>Serguev, 1989$^{29}$</td>
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<td>$\dot{Q}_A/Q_T$</td>
<td>Schrijen, 1979$^{30}$</td>
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<td>$\dot{V}_A/Q_c$</td>
<td>Prefaut, 1980$^{31}$</td>
</tr>
<tr>
<td>3. Humans</td>
<td>Respiratory Failure</td>
<td>$\dot{Q}_A/Q_T$</td>
<td>Rigaud, 1981$^{32}$</td>
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<td></td>
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<td>$\dot{Q}_A/Q_T$</td>
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<td>$\dot{Q}_A/Q_T$</td>
<td>Dull, 1983$^{34}$</td>
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<td>$\dot{Q}_A/Q_T$</td>
<td>Melot, 1983$^{5}$</td>
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<td>$\dot{Q}_A/Q_T$</td>
<td>Tenillon, 1980$^{35}$</td>
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<td></td>
<td></td>
<td>$\dot{Q}_A/Q_T$</td>
<td>Naeije, 1981$^{36}$</td>
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$P_O_2$ = oxygen tension; $P_{AP}$ = pulmonary artery pressure; $P_{VR}$ = pulmonary vascular resistance; $\Delta V_A/Q_c$ = change in ventilation-perfusion ratio; $Q_A/Q_T$ = shunt; $P(A \rightarrow O_2)$ = alveolar arterial oxygen tension difference.

* Changes are indicated by: $+$ increase; $-$ decrease; $\pm$ no change.

High-dose almitrine inhibits HPV

Almitrine differs from regional hypoxia for studying the HPV response in several ways. Models of global hypoxia result in systemic hypoxemia, rather than hypoxia of a lung region. Since the hypoxic segment size is the whole lung, the HPV response is measured only as a perfusion pressure change. During global hypoxia in vivo, Romaldini et al.$^{9}$ infused almitrine in saline at 0.1 mg·kg$^{-1}$·30 min$^{-1}$ into 12 anesthetized and paralyzed closed-chest dogs. They based their conclusion that almitrine enhanced HPV primarily on increases in PVR. During almitrine infusion, PVR increased 77.9% while breathing 12% $O_2$ and 38.4% while breathing 21% $O_2$ when compared to breathing 100% $O_2$. They showed that administering hypoxia and then almitrine caused additional vasoconstriction increasing PAP, but they did not provide evidence of specific enhancement of HPV.

Several other studies of regional hypoxia in vivo have suggested that, in a lung already constricted by HPV, almitrine did not produce further constriction. Barer et al.$^{10}$ observed vasoconstriction by almitrine for all preparations and species during normoxia and for the initial responses during hypoxia or hyperventilation. They found that the effectiveness of HPV was decreased by almitrine in the left lower lobe of cats.

Allison et al.$^{37}$ studied greyhound dogs with generalized as well as lobar hypoxia. In the presence of almitrine (10–39 μg·kg$^{-1}$ iv bolus), PAP, PVR, and CO increased, and specific pulmonary vascular conductance in the closed-chest dogs decreased with 30% and 21% $O_2$, but not with 14% $O_2$. They concluded that, since "almitrine does not produce additional vessel narrowing...it is unlikely to potentiate local hypoxic vasoconstriction."$^{37}$

Hughes et al.$^{12}$ later studied open-chest dogs ($n = 7$) where either 30% $O_2$ or 12.5% $O_2$ was administered to the right retrocardiac lobe while the rest of the lung received 30% $O_2$. Pulmonary vascular conductance decreased with almitrine administration in the lung, whereas it did not change when the lobe was already hypoxic.

Schmoller et al.$^{38}$ studies anesthetized paralyzed dogs in which the lungs were separated by a tracheal divider. During almitrine in saline infusion (0.1 mg·kg$^{-1}$·30 min$^{-1}$), left lung blood flow (%$Q_L$) remained unchanged with $P_{O_2}$ 0.21 and 0.06, so that they concluded that "there was no diversion of blood away from the hypoxic regions." In fact, their dose was the same as that used by Romaldini, which was also the dose used in our preliminary study,$^{24}$ where we also observed that almitrine had no effect on %$Q_L$.

In summary, this study showed that almitrine bismuth ecaused nonspecific pulmonary vasoconstriction that was greatest in vessels with the least initial tone. Thus, almitrine caused greater constriction in 100% $O_2$ ventilated lung than in hypoxic lung regions, and blood flow was diverted from the hypoxic lung back to the hypoxic lung; therefore, the effectiveness of HPV was diminished, while the total pulmonary vascular conduc-
tance was decreased. The hypoxic lung showed no further constriction when almitrine was added, and HPV was not enhanced in the hypoxic lung. Since the hypoxic lung showed no further constriction when almitrine was added and flow diversion was, in fact, blunted, it is unlikely that the improvements of arterial oxygenation that have been reported to follow the administration of almitrine to patients with chronic obstructive lung disease were due to the enhancement of hypoxic pulmonary vasoconstriction.

The authors thank Jonathan Reed, B.S., M.S., Larry Nann, B.S., and Steven Gorman, B.S., for their technical expertise, and Darlene Dickinson for preparation of the manuscript.

References


