

## High-dose Almitrine Bismesylate Inhibits Hypoxic Pulmonary Vasoconstriction in Closed-chest Dogs

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The effect of almitrine bismesylate 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% O<sub>2</sub>, while the left lung was ventilated with either 100% O<sub>2</sub> ("hyperoxia") or with an hypoxic gas mixture ("hypoxia"; end-tidal P<sub>O<sub>2</sub></sub> = 50.1 ± 0.1 mmHg). Cardiac output (CO) was altered from a "normal" value of 3.10 ± 0.18 l · min<sup>-1</sup> to a "high" value of 3.92 ± 0.16 l · min<sup>-1</sup> 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 bismesylate was administered as a constant infusion of 14.3 µg · kg<sup>-1</sup> · min<sup>-1</sup> for a mean plasma concentration of 219.5 ± 26.4 ng · ml<sup>-1</sup>. Relative blood flow to each lung was measured with a differential CO<sub>2</sub> excretion (V̇CO<sub>2</sub>) method corrected for the Haldane effect. With both lungs hyperoxic, the percent left lung blood flow (%Q<sub>L-V̇CO<sub>2</sub></sub>) was 44 ± 1%. When the left lung was exposed to hypoxia, the %Q<sub>L-V̇CO<sub>2</sub></sub> decreased significantly to 22 ± 1%. However, with the administration of almitrine, the %Q<sub>L-V̇CO<sub>2</sub></sub> during left lung hypoxia increased significantly to 36 ± 2%. The arterial oxygen tension decreased significantly between hyperoxia (P<sub>aO<sub>2</sub></sub> = 633 ± 6 mmHg) and hypoxia (271 ± 31 mmHg). With the addition of almitrine, there was no change during hyperoxia; however, during hypoxia, the P<sub>aO<sub>2</sub></sub> decreased significantly to 124 ± 15 mmHg. 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 (G<sub>R</sub> × 10<sup>5</sup>) (1.6 ± 0.1 dyn<sup>-1</sup> · cm<sup>5</sup> · s<sup>-1</sup>) did not change significantly during hyperoxia or hypoxia when no drug was given. With the administration of almitrine, G<sub>R</sub> decreased significantly to 1.0 ± 0.1 dyn<sup>-1</sup> · cm<sup>5</sup> · s<sup>-1</sup> during both hyperoxia and hypoxia. The same was true at normal and high cardiac output. The pulmonary vascular conductance of the left lung (G<sub>L</sub>) decreased significantly between hyperoxia (1.24 ± 0.1 dyn<sup>-1</sup> · cm<sup>5</sup> · s<sup>-1</sup>) and hypoxia (0.7 ± 0.1 dyn<sup>-1</sup> · cm<sup>5</sup> · s<sup>-1</sup>). However, with the addition of almitrine, G<sub>L</sub> decreased significantly during hyperoxia (0.8 ± 0.1 dyn<sup>-1</sup> · cm<sup>5</sup> · s<sup>-1</sup>), but not during hypoxia (0.8

± 0.1 dyn<sup>-1</sup> · cm<sup>5</sup> · s<sup>-1</sup>). The same was true at normal and high cardiac output. It is concluded that almitrine bismesylate caused non-specific pulmonary vasoconstriction that was greater in the 100% O<sub>2</sub> ventilated lung than in the hypoxic lung regions. Therefore, blood flow was diverted from the hyperoxic back to the hypoxic lung causing a reduction of the HPV response. (Key words: Almitrine bismesylate. Hypoxia: pulmonary vascular response. Lung: blood flow; hypoxic pulmonary vasoconstriction; shunting; vascular conductance. Oxygen: blood levels.)

ALMITRINE BISMESYLATE stimulates peripheral chemoreceptors,<sup>1,2</sup> thus increasing ventilatory response to hypoxia.<sup>3-5</sup> However, interest in the pulmonary vasomotor effects of almitrine bismesylate 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 (V̇<sub>E</sub>) which nearly always occur.<sup>6-8</sup> Based on indirect evidence, investigators have both proposed<sup>6,9</sup> and denied<sup>10-14</sup> that enhancement of hypoxic pulmonary vasoconstriction (HPV) by almitrine bismesylate is a possible mechanism for this improvement in gas exchange. The present study examined this controversy and tested the effect of almitrine bismesylate 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<sup>-1</sup> 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<sup>-1</sup> intravenous pancuronium supplemented with 0.2-0.5 mg/30 min.

After subcricoid tracheostomy, a double-lumen Kottmeier® endobronchial tube (Rüsch 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% O<sub>2</sub> ventilation was used to confirm

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Received from the McNeil Center for Research in Anesthesia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. Accepted for publication May 21, 1987. Supported in part by ASA Starter Grant and by National Institute of General Medical Sciences Grants #GM 29628 & GM 07612.

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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% O<sub>2</sub> via a Harvard® dual-piston respirator with 5 cm H<sub>2</sub>O 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 H<sub>2</sub>O. Inspired CO<sub>2</sub> and/or the respiratory rate were adjusted to keep right and left end-tidal P<sub>CO<sub>2</sub></sub> 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<sub>O<sub>2</sub></sub> and P<sub>CO<sub>2</sub></sub> 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 euolemia (285 ± 26 ml · h<sup>-1</sup> Normosol® and/or 0.9% saline) and for infusion of almitrine bismesylate. Almitrine was administered at a constant infusion of 14.3 µg · kg<sup>-1</sup> · min<sup>-1</sup> (Harvard® Infusion Pump model #600-910/920). Body temperature, measured by an esophageal temperature probe, was maintained at 38 ± 0.2° C with heating lamps, pads, and heated humidifier. Sodium bicarbonate (NaHCO<sub>3</sub>) 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® #93A-131H-7F). Pressures were measured continuously on an 8-channel Grass® polygraph (Model #7WC16PA 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 H<sub>2</sub>O, as appropriate. Thermodilution cardiac outputs (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 ID arterial end, 6 mm ID 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-

TABLE 1. Study Design

|                                                | Cardiac Output |        |
|------------------------------------------------|----------------|--------|
|                                                | Normal         | High   |
| A. Almitrine<br>100% O <sub>2</sub><br>Hypoxia | a<br>b         | c<br>d |
| B. Wait                                        |                |        |
| C. Control<br>100% O <sub>2</sub><br>Hypoxia   | e<br>f         | g<br>h |

lated with approximately 300 units · kg<sup>-1</sup> of heparin iv, followed by 50 units · kg<sup>-1</sup> every 30 min.

Relative blood flow to each lung was measured with a differential carbon dioxide elimination ( $\dot{V}CO_2$ ) method.<sup>15,16</sup> 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® #4016). Carbon dioxide (CO<sub>2</sub>) production was calculated continuously from the expired volume signals and from the difference between the inspired and mixed-expired CO<sub>2</sub> concentration. The excretion was corrected for the Haldane effect when one lung was ventilated with a hypoxic gas mixture.<sup>17</sup> The left lung blood flow (% $\dot{Q}_{L-\dot{V}CO_2}$ ) was calculated as the product of the relative CO<sub>2</sub> 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% O<sub>2</sub>, 5% CO<sub>2</sub>, bal N<sub>2</sub>) ventilation to the left lung were alternated with 100% O<sub>2</sub> ventilation to determine the presence of stable reproducible pulmonary blood flow and pressure responses to hypoxia.<sup>18</sup>

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% O<sub>2</sub>, while the left lung was ventilated either with 100% O<sub>2</sub> (hyperoxia) or with an hypoxic gas mixture (hypoxia). With a flow meter (Matheson model #7481T

series R7400) to control inspired  $O_2$ ,  $CO_2$ , and  $N_2$ , the left lung end-tidal  $P_{O_2}$  during hypoxia was maintained at 50 mmHg; this was chosen to yield an oxygen tension at the sensor site for HPV ( $P_{SO_2}$ ) that would be approximately a half maximal hypoxic stimulus.<sup>19</sup>

Almitrine bismesylate was dissolved in its solvent, malic acid, and diluted with 0.9% saline solution. It was administered as a constant infusion of  $14.3 \mu g \cdot kg^{-1} \cdot min^{-1}$ .

### MEASUREMENTS

At each phase, the following measurements were made: peak and mean airway ( $P_{aw}$ ), 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  $O_2$  and  $CO_2$  of each lung by mass spectrometer. Arterial and mixed venous blood gas samples were collected to determine pH,  $P_{O_2}$ ,  $P_{CO_2}$  (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 Chromatograph Series #10; Perkin-Elmer® LC-93 UV/Visible Spectrophotometer Detector).<sup>20</sup> Right and left tidal volume ( $V_T$ ), respiratory rate (RR), and minute ventilation ( $\dot{V}_E$ ) were recorded.

### CALCULATIONS

From the recorded data, blood flow, vascular conductance, 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 ( $dyn^{-1} \cdot cm^5 \cdot s^{-1}$ ) were calculated from the respective lung blood flow in  $l \cdot min^{-1}$  divided by the perfusion pressure in mmHg ( $\times 80$ ).

Alveolar oxygen tension ( $PA_{O_2}$ ) for the right lung ventilated with 100%  $O_2$  was calculated from the barometric pressure minus the saturated water vapor pressure minus the  $PA_{CO_2}$ . During hypoxic ventilation, the addition of  $CO_2$  to the inspired gas was sufficient to introduce errors into the alveolar gas mixing equation.<sup>21</sup> Therefore, left lung  $PA_{O_2}$  was calculated as the mean of the measured mixed expired  $P_{O_2}$  and the mixed venous  $P\bar{V}_{O_2}$ . 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:

$$CO_2 = (1.34 \times Hb \times \% Sat) + (P_{O_2} \times 0.0031)$$

Per cent saturation (% Sat), corrected for pH and temperature, was calculated from a nomogram for canine hemoglobin.<sup>22</sup>

Calculation of left lung blood flow was made by two methods. The first method, based on differential  $CO_2$  excretion of each lung, was described above as  $\% \dot{Q}_L \cdot \dot{V}_{CO_2}$ . The second method for estimation of left lung blood flow during the hypoxic periods ( $\% \dot{Q}_{LVA}$ ) was based on a variation of the traditional shunt equation which allowed for the difference between alveolar oxygen tension of the hypoxic *versus* hyperoxic lung.<sup>21,23</sup> This equation assumed: 1) that the total anatomic shunt flow ( $\dot{Q}_S/\dot{Q}_T$ ) measured during 100%  $O_2$  ventilation remained unchanged during hypoxic ventilation 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%  $O_2$  ventilation were small compared to the variations in left lung flow during the experimental conditions. The stimulus for HPV, the  $P_{SO_2}$ ,<sup>19</sup> was calculated from:

$$P_{SO_2} = (P\bar{V}_{O_2})^{0.32} \times (PA_{O_2})^{0.68}$$

### 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 responses 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  $\pm$  standard error.

### Results

Since the general experimental conditions for pHa,  $Pa_{CO_2}$ , temperature, hemoglobin (Hb), SAP, CVP, airway pressure right lung ( $P_{awR}$ ), airway pressure left lung ( $P_{awL}$ ), minute ventilation right lung ( $\dot{V}_{ER}$ ), and minute ventilation left lung ( $\dot{V}_{EL}$ ) did not change significantly between the eight phases of the study, only the control measurements made during the 100%  $O_2$ -normal cardiac output-no almitrine phase are presented in table 2. The mean heart rate (HR) during the 100%  $O_2$ -normal cardiac output state was  $184 \pm 10$  bpm, and varied between  $179 \pm 9$  bpm to  $200 \pm 12$  bpm. The mean systemic vascular resistance (SVR) decreased significantly for each normal/high cardiac output pair (3774

$\pm 284$  to  $2872 \pm 131$  dyn·cm<sup>-5</sup>·s), 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 (PaO<sub>2</sub>) decreased in the presence of almitrine at both levels of cardiac output. Mixed venous oxygen tension (PvO<sub>2</sub>) increased significantly between normal/high output pair, but was not affected by almitrine. During hypoxia, the alveolar PAO<sub>2</sub> were not significantly different. During hypoxia, the P<sub>SO<sub>2</sub></sub>, the stimulus for HPV, increased significantly when the cardiac output increased; however, at each cardiac output level, the P<sub>SO<sub>2</sub></sub> decreased significantly when almitrine was given.

The plasma concentration of almitrine bismesylate 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% O<sub>2</sub>-Normal Cardiac Output-No Almitrine Condition (n = 7, Mean  $\pm$  SE)

|                                         |                   |
|-----------------------------------------|-------------------|
| pHa                                     | 7.353 $\pm$ 0.009 |
| PaCO <sub>2</sub> (mmHg)                | 39.2 $\pm$ 0.6    |
| temp (°C)                               | 38.0 $\pm$ 0.2    |
| Hb (g·dl <sup>-1</sup> )                | 12.8 $\pm$ 0.3    |
| SAP (mmHg)                              | 147.9 $\pm$ 3.7   |
| CVP (mmHg)                              | 5.0 $\pm$ 0.5     |
| P <sub>awR</sub> (cm H <sub>2</sub> O)  | 11.2 $\pm$ 0.2    |
| P <sub>awL</sub> (cm H <sub>2</sub> O)  | 11.0 $\pm$ 0.2    |
| TV <sub>R</sub> (ml·min <sup>-1</sup> ) | 218 $\pm$ 2       |
| TV <sub>L</sub> (ml·min <sup>-1</sup> ) | 202 $\pm$ 7       |
| V <sub>ER</sub> (ml·min <sup>-1</sup> ) | 3969 $\pm$ 102    |
| V <sub>EL</sub> (ml·min <sup>-1</sup> ) | 3700 $\pm$ 232    |

pHa = arterial pH; PaCO<sub>2</sub> = arterial carbon dioxide tension; temp = temperature; Hb = hemoglobin; SAP = mean systemic arterial pressure; CVP = mean central venous pressure; P<sub>awR</sub> = mean airway pressure right lung; P<sub>awL</sub> = mean airway pressure left lung; TV<sub>R</sub> = tidal volume right lung; TV<sub>L</sub> = tidal volume left lung; V<sub>ER</sub> = minute ventilation right lung; V<sub>EL</sub> = minute ventilation left lung.

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

During both hyperoxia 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% O<sub>2</sub>/hypoxia and Normal (NI)/high (Hi) Cardiac Outputs (n = 7, Mean  $\pm$  standard error)

|                                                                                         | 100% O <sub>2</sub> |               |              |               | Hypoxia      |               |              |               |
|-----------------------------------------------------------------------------------------|---------------------|---------------|--------------|---------------|--------------|---------------|--------------|---------------|
|                                                                                         | No Almitrine        |               | Almitrine    |               | No Almitrine |               | Almitrine    |               |
|                                                                                         | NI                  | Hi            | NI           | Hi            | NI           | Hi            | NI           | Hi            |
| CO (l/min)                                                                              | 3.10<br>0.18        | 3.92†<br>0.16 | 2.81<br>0.19 | 3.58†<br>0.15 | 3.12<br>0.20 | 3.98†<br>0.26 | 3.09<br>0.23 | 3.95†<br>0.20 |
| PaO <sub>2</sub> (mmHg)                                                                 | 633<br>6            | 637<br>4      | 633<br>5     | 624<br>13     | 271<br>31    | 260<br>29     | 124*<br>15   | 139*<br>9     |
| PvO <sub>2</sub> (mmHg)                                                                 | 69<br>1             | 79†<br>1      | 65<br>3      | 79†<br>3      | 61<br>2      | 67†<br>1      | 53*<br>2     | 61*†<br>1     |
| PAO <sub>2</sub> (mmHg)                                                                 |                     |               |              |               | 50<br>1      | 51<br>1       | 50<br>1      | 50<br>1       |
| P <sub>SO<sub>2</sub></sub> (mmHg)                                                      |                     |               |              |               | 54<br>1      | 57†<br>1      | 51*<br>1     | 54*†<br>1     |
| PAP (mmHg)                                                                              | 21<br>1             | 23<br>1       | 28*<br>2     | 32*<br>3      | 24<br>1      | 28<br>1       | 31*<br>2     | 33*<br>2      |
| PAOP (mmHg)                                                                             | 7<br>1              | 8<br>1        | 7<br>1       | 9<br>1        | 8<br>1       | 8<br>1        | 9<br>1       | 9<br>1        |
| G <sub>R</sub> (10 <sup>-3</sup> ·dyn <sup>-1</sup> ·cm <sup>5</sup> ·s <sup>-1</sup> ) | 1.6<br>0.1          | 1.9<br>0.1    | 1.0*<br>0.1  | 1.2*<br>0.2   | 1.8<br>0.1   | 1.9<br>0.1    | 1.0*<br>0.1  | 1.3*<br>0.2   |
| G <sub>L</sub> (10 <sup>-3</sup> ·dyn <sup>-1</sup> ·cm <sup>5</sup> ·s <sup>-1</sup> ) | 1.2<br>0.1          | 1.4<br>0.1    | 0.8*<br>0.1  | 0.9*<br>0.1   | 0.7<br>0.1   | 0.8<br>0.2    | 0.8<br>0.1   | 0.8<br>0.1    |
| %VA                                                                                     | 2.7<br>0.6          | 2.7<br>0.3    | 2.6<br>0.3   | 3.7<br>1.1    |              |               |              |               |
| %Q <sub>LVA</sub>                                                                       |                     |               |              |               | 19.7<br>2.2  | 20.3<br>2.0   | 35.7*<br>2.3 | 31.1*<br>1.1  |
| %Q <sub>LVC</sub>                                                                       | 44<br>1             | 44<br>1       | 45<br>1      | 44<br>2       | 22<br>1      | 23<br>2       | 36*<br>2     | 30*<br>2      |
| Almitrine plasma concentration (ng·ml <sup>-1</sup> )                                   | 18<br>8             | 16<br>6       | 257*<br>54   | 274*<br>45    | 16<br>7      | 13<br>7       | 286*<br>56   | 319*<br>54    |

\* 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).

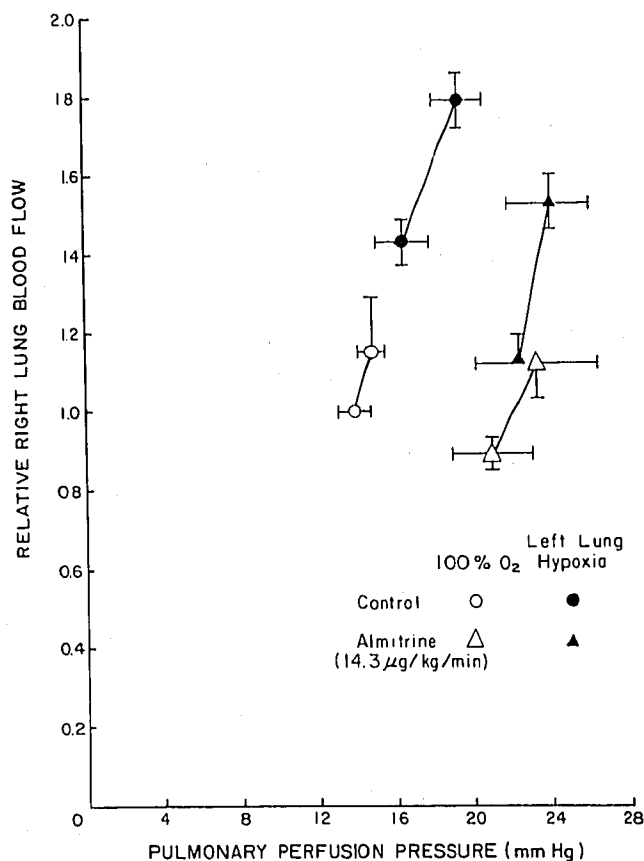


FIG. 1. Pressure-flow relationship for the right lung. The blood flow to the right lung was calculated relative to the 100% O<sub>2</sub>-normal cardiac output-no almitrine phase. Compared to the control state when almitrine was absent (circles), the addition of almitrine (triangles) caused vasoconstriction 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<sub>2</sub>, 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.

creases 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 ( $7 \pm 1$  mmHg) versus the hypoxia-normal cardiac output and hypoxia-high cardiac output groups with almitrine ( $9 \pm 1$  mmHg).

There was no change in percent venous admixture (%VA) during 100% O<sub>2</sub> ventilation. The percent left lung blood flow (% $\dot{Q}_{L-VA}$ ) during hypoxia increased with the administration of almitrine.

Percent left lung blood flow (% $\dot{Q}_{L-VCO_2}$ ) decreased significantly between 100% O<sub>2</sub> ventilation and hypoxia. During hypoxia, almitrine administration caused a significant increase in % $\dot{Q}_{L-VCO_2}$ .

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<sub>2</sub> 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<sub>2</sub> 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.

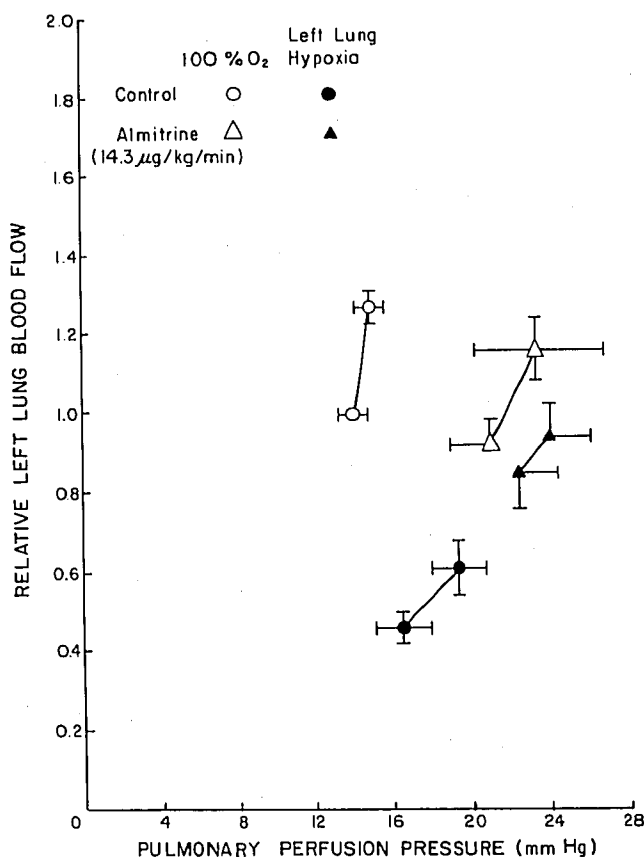


FIG. 2. Pressure-flow relationship for the left lung. The blood flow to the left lung was calculated relative to the 100% O<sub>2</sub>-normal cardiac output-no almitrine phase. In the absence of almitrine (circles), active HPV was represented by a rightward and downward shift of the points from hyperoxia (open circles) to hypoxia (filled circles). With the addition of almitrine (triangles), there was constriction of the hyperoxic 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 lung 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 ( $P < 0.004$ ;  $R = -0.55$ ).

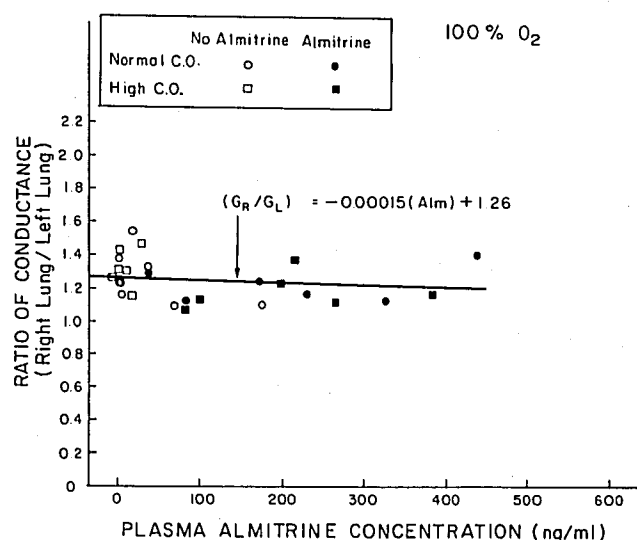


FIG. 3. Effect of almitrine concentration on ratio of pulmonary vascular conductances of the right lung/left lung ( $G_R/G_L$ ) during 100%  $O_2$  ventilation. When both lungs were ventilated with 100%  $O_2$ , the addition of almitrine caused both lungs to constrict, so that the ratio of pulmonary vascular conductances of the right lung/left lung ( $G_R/G_L$ ) did not change. 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).

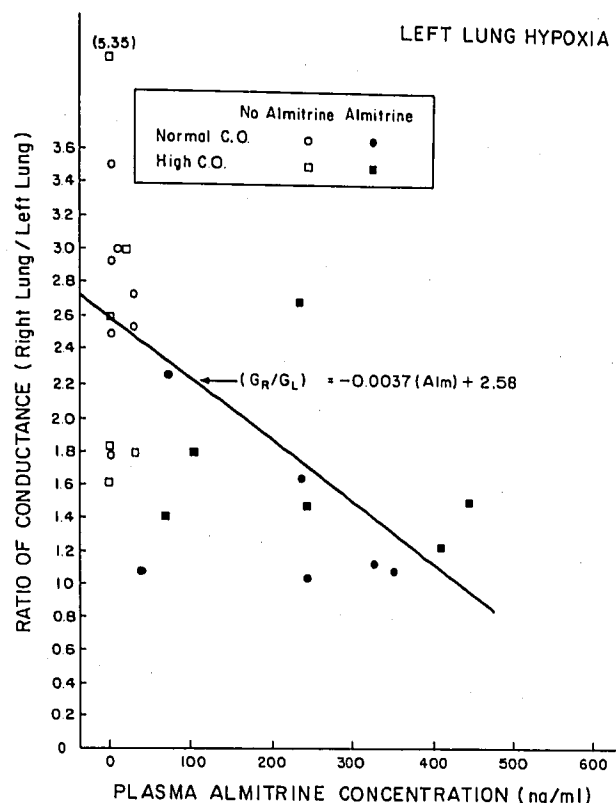


FIG. 4. Effect of almitrine concentration on the ratio of pulmonary vascular conductances of the right lung/left lung ( $G_R/G_L$ ) during hypoxia. The pulmonary vascular conductance of the right lung ( $G_R$ ) which was hyperoxic during left lung hypoxia diminished with the addition of almitrine. The 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.<sup>24</sup> In that study, the left lung end-tidal oxygen tension ( $P_{ETO_2}$ ) during hypoxia was  $29.0 \pm 0.5$  mmHg and the almitrine infusion was  $3.3 \mu g \cdot kg^{-1} \cdot min^{-1}$ . This dose was the same as that used by Romaldini *et al.*,<sup>9</sup> who suggested that almitrine enhanced HPV. In our study, almitrine administered at this rate yielded a final plasma concentration of  $52.9 \pm 4.4$  ng  $\cdot ml^{-1}$  and had no consistent effect on the HPV response or on the pulmonary vascular conductance of

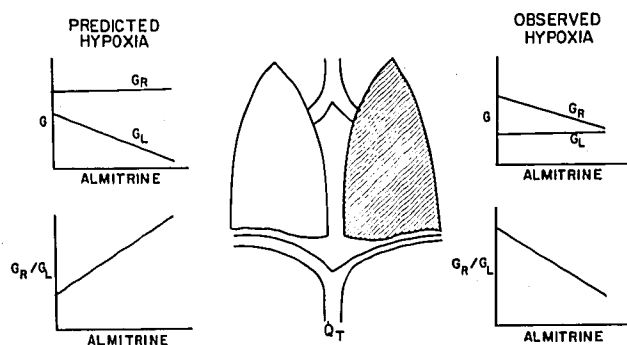


FIG. 5. Predicted *versus* observed outcome for the effect of almitrine. If almitrine had enhanced HPV, as predicted, and had had no effect on the hyperoxic lung, 1) the pulmonary vascular conductance of the hyperoxic right lung ( $G_R$ ) would have remained unchanged; 2) the pulmonary vascular conductance 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 hyperoxic 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.

either lung, whether hyperoxic or hypoxic. Therefore, for the present study, a larger dose of almitrine was chosen, so that almitrine was administered at a constant infusion of  $14.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Routes of administration and dosage vary in literature for any given species. Routes have been *per os*, intravenous bolus, and intravenous infusion, and doses have ranged from  $0.25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ <sup>5,10</sup> to a total dose of  $3 \text{ mg} \cdot \text{kg}^{-1}$ .<sup>10</sup> The solvent for almitrine, malic acid, has been reported to have no effect.<sup>10,14</sup> Malic acid is a normal constituent of blood [ $0.5 (0.1\text{--}0.9) \text{ mg}/100\text{ml}$ ].<sup>25,26</sup>

The present study has determined that, with the larger dose, almitrine acted as a nonspecific vasoconstrictor with a predominant effect on the least hypoxic lung. Pressure-flow lines allow the two major responses of HPV to be demonstrated on the same graph. In the right lung, which was always hyperoxic, the administration of almitrine caused vasoconstriction whether the left lung was hyperoxic or hypoxic (fig. 1). This vasoconstriction was represented by a shift to the right of the pressure-flow line with the addition of almitrine. Relative blood flow was used to more easily compare the left lung to the right lung; the relative blood flow of 1.0 was defined by dividing the blood flow of each phase by the control 100%  $\text{O}_2$ -normal cardiac output-no almitrine blood flow for each lung. In the left lung, the addition of almitrine caused vasoconstriction when the left lung was ventilated with 100%  $\text{O}_2$ , but no further constriction was detected when the left lung was already hypoxic (fig. 2).

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 hyperoxic 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 hyperoxic 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 ( $P_{\text{SO}_2}$ ), which is the oxygen tension at the sensor for HPV, is related to both the alveolar oxygen tension ( $P_{\text{AO}_2}$ ) and the mixed venous oxygen tension ( $P\bar{v}\text{O}_2$ ).<sup>19</sup> Although the  $P_{\text{AO}_2}$  was held constant during hypoxia, the  $P\bar{v}\text{O}_2$  and  $P_{\text{aO}_2}$  decreased significantly with the administration of almitrine. Consequently, the  $P_{\text{SO}_2}$  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 hyperoxic 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,  $P_{\text{aO}_2}$  and %VA, and  $\dot{V}_E$  (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.<sup>36</sup> 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  $P_{\text{aO}_2}$  and reduction of %VA might have been related to increases in cardiac output increasing  $P\bar{v}\text{O}_2$  or to improved perfusion to areas with an increased alveolar ventilation ( $\dot{V}_A$ ). 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

| Species   | Condition           | Result*                                            | Reference                     |
|-----------|---------------------|----------------------------------------------------|-------------------------------|
| 1. Humans | Healthy             | $1P_{O_2}$                                         | Guillerm, 1974 <sup>27</sup>  |
| 2. Humans | COPD                | $1P_{O_2}$                                         | Powles, 1983 <sup>7</sup>     |
|           |                     | $1P_{O_2}$                                         | Neukirch, 1974 <sup>28</sup>  |
|           |                     | $1P_{O_2}$                                         | Sergysels, 1980 <sup>29</sup> |
|           |                     | $1P_{O_2} \pm PAP \pm PVR$                         | Schrijen, 1978 <sup>30</sup>  |
|           |                     | $P_{O_2}$                                          | Prefaut, 1980 <sup>31</sup>   |
|           |                     | $1P_{O_2}$                                         | Rigaud, 1981 <sup>32</sup>    |
|           |                     | $1P_{O_2} \pm PVR \Delta \dot{V}_A / \dot{Q}_C$    | Castaing, 1981 <sup>33</sup>  |
|           |                     | $\pm P_{O_2} \quad 1PAP \quad 1PVR$                | Dull, 1983 <sup>8</sup>       |
| 3. Humans | Respiratory Failure | $1P_{O_2} \quad 1PVR \Delta \dot{V}_A / \dot{Q}_C$ | Melot, 1983 <sup>6</sup>      |
|           |                     | $1P_{O_2} \pm PAP \quad 1PVR$                      | Tenaillon, 1980 <sup>34</sup> |
|           |                     | $1P_{O_2} \pm PAP \pm PVR$                         | Nacjie, 1981 <sup>35</sup>    |

$P_{O_2}$  = oxygen tension; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance;  $\Delta \dot{V}_A / \dot{Q}_C$  = change in ventilation-perfusion ratio;  $\dot{Q}_S / \dot{Q}_T$  = shunt;  $P_{(A-a)O_2}$  = alveolar arte-

rial oxygen tension difference.

\* Changes are indicated by: 1 = increase; l = decrease;  $\pm$  = no change.

poxia 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.*<sup>9</sup> infused almitrine in saline at  $0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot 30 \text{ min}^{-1}$  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 59.7% 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 product further constriction. Barer *et al.*<sup>10</sup> observed vasoconstriction by almitrine for all preparations and species during normoxia and for the initial responses during hypoxia or hypoventilation. They found that the effectiveness of HPV was decreased by almitrine in the left lower lobe of cats.

Allison *et al.*<sup>37</sup> studied greyhound dogs with generalized as well as lobar hypoxia. In the presence of almitrine ( $10\text{--}33 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$  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."<sup>37</sup>

Hughes *et al.*<sup>13</sup> 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.*<sup>38</sup> studies anesthetized paralyzed dogs in which the lungs were separated by a tracheal divider. During almitrine in saline infusion ( $0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot 30 \text{ min}^{-1}$ ), left lung blood flow ( $\% \dot{Q}_L$ ) remained unchanged with  $FI_{O_2}$  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,<sup>24</sup> where we also observed that almitrine had no effect on  $\% \dot{Q}_L$ .

In summary, this study showed that almitrine bismesylate caused 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 hyperoxic lung back to the hypoxic lung; therefore, the effectiveness of HPV was diminished, while the total pulmonary vascular conductance 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.

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