EFFECTS OF SELECTIVE ALPHA<sub>1</sub>-ADRENOCEPTOR BLOCKADE IN DOGS WITH HYPOXIC PULMONARY VASOCONSTRICTION

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The acute effects of the selective alpha<sub>1</sub>-blocker, E-643 (Bunazosine), on experimental pulmonary hypertension (PH) caused by hypoxic pulmonary vasoconstriction (HPV) in mongrel dogs were examined. Ninety-second ventilation with 5% O<sub>2</sub> and 95% N<sub>2</sub> was used for hypoxic stimulation. The effects of E-643 were evaluated at doses of 1, 5, 10, 20 and 50 μg/kg in this order until the systemic arterial mean pressure (SAm) had decreased by 20 mmHg when compared with the control value during room air ventilation. PaO<sub>2</sub> and PaCO<sub>2</sub> decreased by 64.6 ± 11.0 Torr and 2.4 ± 2.5 Torr, respectively, and the pH increased by 0.031 ± 0.012 during hypoxic ventilation. These blood gas changes affected during hypoxic stimulation were almost the same before E-643 administration. Progression of arterial blood hypoxemia due to E-643 administration during room air ventilation was not observed. SAm decreased by 8.0 ± 11.9 mmHg after E-643 administration, while left atrial mean pressure (LAm) and cardiac output (CO) did not change significantly. Prior to E-643 administration, mean pulmonary arterial pressure (PAm) and pulmonary vascular resistance (PVR) increased by 6.4 ± 3.3 mmHg and 6.2 ± 3.8 HRU, respectively, during the 90 sec hypoxic ventilation period. After E-643 administration, the increases in PAm and PVR were 3.9 ± 1.7 mmHg and 3.3 ± 2.3 HRU, respectively. The supression of increases in PAm and PVR was significant.

The conclusion is that E-643, a selective alpha<sub>1</sub>-blocker, is effective at restraining HPV in the dog model.

Both alpha- and beta-adrenergic receptors are present in normal adult pulmonary circulation, similar to those seen in vascular smooth muscle in the systemic circulation<sup>1–4</sup>. Alpha-receptors appear to predominate under normal conditions at rest, however, under a state of increased vascular tone—as elicited by acute hypoxia or under other stressful conditions, the reverse is true<sup>2,5</sup>. There are few reports on the effects of alpha-blockers, such as phenoxybenzamine and phentolamine, on pulmonary vascular tone. One group of studies described the effectiveness of alpha-blockers on pulmonary hypertension with hypoxia<sup>2,3,6</sup> while others indicated that these drugs were not effective<sup>7–10</sup>. Therefore, the effects of alpha-blockade on pulmonary circulation remain controversial.

Recently, selective alpha<sub>1</sub>-adrenoceptor blockers were used in systemic hypertension therapy<sup>11,12</sup>. They have the advantage of blocking only alpha<sub>1</sub>-adrenoceptors without blocking alpha<sub>2</sub>-adrenoceptors. The release of noradrenaline from the sympathetic nerve ending is not activated by alpha<sub>1</sub>-blockers, so the vasoconstric-
The action of noradrenaline is suppressed.\textsuperscript{13-15} Alpha\textsubscript{1}-adrenoceptor blockers may be effective for hypoxic pulmonary vasoconstriction (HPV) for which there are few effective drugs without nitroglycerin.

This study was carried out in order to study the acute effects of selective alpha\textsubscript{1}-blockade on hypoxic pulmonary vasoconstriction in dogs.

**METHODS**

Nine mongrel dogs weighing 10–15 kg were anesthetized with sodium pentobarbital (30–35 mg/kg, iv). Supplemental doses of 5–10 mg/kg were given when necessary. Endotracheal intubation was performed and positive pressure ventilation was administered with a volume type respirator using a tidal volume 15–20 ml/kg and a frequency of 16–20 breaths per minute. The expiratory tube from the respirator was placed under 5 cm of water in order to maintain expansion of the lungs upon opening the chest. Minute ventilation was adjusted to maintain arterial PCO\textsubscript{2} (PaCO\textsubscript{2}) levels between 30–40 Torr and arterial pH levels were maintained between 7.300–7.500 during the experiments. Polyethylene catheters were inserted into both femoral arteries for the arterial blood sampling and measurements of arterial pressure, and into both peripheral veins for drug administration. PO\textsubscript{2} electrode which was connected to the PO\textsubscript{2} monitor system (Searle Med. Products Co., USA)
Fig. 2. Changes in $\text{PaO}_2$ during hypoxic ventilation before and after E-643 administration.

Fig. 3. Changes in $\text{PaCO}_2$ during hypoxic ventilation before and after E-643 administration.

was inserted from left external carotid artery to descending aorta for monitoring $\text{PaO}_2$ changes. The chest was opened by a central sternum incision to allow the measurement of pulmonary arterial pressure, left atrial pressure via cannulas inserted into the vessels of the left upper lobe, and main pulmonary arterial flow using an electromagnetic flowmeter (Nihon Koden Co., Tokyo) attached to the pulmonary arterial trunk. Each catheter for measuring pressure was connected to a P23Db Statham transducer. The hydrostatic level of reference for the pressures was approximately the level of the right atrium. Inspired and expired gas concentrations were monitored in the tracheal tube using a mass spectrometer (MGA 1100B, Perkin Elmer Med. Instruments, Pomona, California). Arterial blood samples for blood gas analysis were collected anaerobically in heparinized syringes from the femoral artery, and arterial $\text{PO}_2$ ($\text{PaO}_2$), $\text{PaCO}_2$ and arterial $\text{pH}$ were measured using an IL1303 blood gas analyzer (Instrument Laboratory, Inc., Lexington, MA, USA). Pulmonary vascular resistance (PVR) was calculated, using a signal processor (7T17, Nihon Denki-San-ei Co., Tokyo), as the quotient of the mean pressure difference between the pulmonary artery and the left atrium, and pulmonary blood flow. PVR was reported in hybrid resistance units (HRU).

After verification of hemodynamic stability, ventilatory and blood gas parameters during room air ventilation, the systemic artery (SAM), pulmonary artery (PAm) and left atrium (LAm) mean pressure, pulmonary blood flow (CO), pH, $\text{PaO}_2$, $\text{PaCO}_2$ were measured. Thereafter, the dog was ventilated with a gas mixture con-

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sisting of 5% O₂ and 95% N₂ for 90 sec. The same parameters were measured at the end of 90 sec. of hypoxic ventilation and compared with those for room air ventilation. These values served as the baseline/control state values of the hypoxic response. After baseline room air ventilation and a 90 sec. measurement of each parameter were carried out, room air ventilation was restarted. If control values were reestablished, the dogs were treated with a 1 µg/kg i.v. bolus of E-643 (Bunazosin; Eizai Pharmaceutical Co., Tokyo).

Five minutes after the injection of E-643 and verification of the stabilization of each parameter, the second 90 sec ventilation period with 5% O₂ commenced. The changes in all parameters at the end of the 90 sec hypoxia were measured. The effects of E-643 were evaluated at the doses of 5, 10, 20 and 50 µg/kg E-643 (given in this order) until the SAm had decreased by 20 mmHg compared to control values during room air ventilation (Fig. 1).

Results are expressed as mean ± 1 SD. Statistical comparison of the pre- and post-hypoxic paired values was conducted using the Student’s t-test. Differences were considered to be significant at p < 0.05.

RESULTS

1. Changes in blood gas data

The mean dose of E-643 which decreased the SAm by 20 mmHg was 19.7 ± 18.9 µg/kg.

Prior to E-643 administration, the 90 sec hypoxia induced by 5% O₂ decreased the PaO₂ value from 98.6 ± 7.3 Torr to 33.2 ± 3.8 Torr. The average decline in PaO₂ was 65.4 ± 5.1 Torr (Fig. 2). Mean PaCO₂ during room air ventilation

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TABLE I INCREASE IN PAm (mmHg) DURING HYPOXIA BEFORE AND AFTER E-643 ADMINISTRATION

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Control</th>
<th></th>
<th></th>
<th>After E-643</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Room air</td>
<td>5% O₂</td>
<td>ΔPAm</td>
<td>Room air</td>
<td>5% O₂</td>
<td>ΔPAm</td>
</tr>
<tr>
<td>1</td>
<td>13.9</td>
<td>23.6</td>
<td>9.7</td>
<td>10.8</td>
<td>14.1</td>
<td>3.3</td>
</tr>
<tr>
<td>2</td>
<td>23.1</td>
<td>29.1</td>
<td>6.0</td>
<td>19.9</td>
<td>25.3</td>
<td>5.4</td>
</tr>
<tr>
<td>3</td>
<td>26.3</td>
<td>37.7</td>
<td>11.4</td>
<td>25.6</td>
<td>27.1</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>27.4</td>
<td>37.8</td>
<td>10.4</td>
<td>25.8</td>
<td>31.3</td>
<td>5.5</td>
</tr>
<tr>
<td>5</td>
<td>14.3</td>
<td>19.4</td>
<td>5.1</td>
<td>13.4</td>
<td>18.7</td>
<td>5.3</td>
</tr>
<tr>
<td>6</td>
<td>15.3</td>
<td>17.9</td>
<td>2.6</td>
<td>14.3</td>
<td>16.8</td>
<td>2.5</td>
</tr>
<tr>
<td>7</td>
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<td>14.8</td>
<td>2.7</td>
<td>12.4</td>
<td>15.7</td>
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</tr>
<tr>
<td>8</td>
<td>19.1</td>
<td>22.7</td>
<td>3.6</td>
<td>19.1</td>
<td>21.6</td>
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<td>21.0</td>
<td>6.2</td>
<td>16.3</td>
<td>22.4</td>
<td>6.1</td>
</tr>
<tr>
<td>Mean</td>
<td>18.5</td>
<td>24.9</td>
<td>6.4</td>
<td>17.5</td>
<td>21.4</td>
<td>3.9*</td>
</tr>
<tr>
<td>± 1 SD</td>
<td>5.8</td>
<td>8.3</td>
<td>3.3</td>
<td>3.5</td>
<td>5.7</td>
<td>1.7</td>
</tr>
</tbody>
</table>

(∗p < 0.05)

TABLE II DIFFERENCES IN HEMODYNAMIC VARIABLES FOR EACH DOG DURING A 90 SEC. INHALATION OF 5% O₂ BEFORE AND AFTER E-643 ADMINISTRATION

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Control</th>
<th></th>
<th></th>
<th>After E-643</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ΔLAm (mmHg)</td>
<td>ΔCO (L/min)</td>
<td>ΔPVR (HRU)</td>
<td>ΔLAm (mmHg)</td>
<td>ΔCO (L/min)</td>
<td>ΔPVR (HRU)</td>
</tr>
<tr>
<td>1</td>
<td>-0.7</td>
<td>-0.02</td>
<td>10.9</td>
<td>-0.2</td>
<td>-0.01</td>
<td>6.0</td>
</tr>
<tr>
<td>2</td>
<td>-0.1</td>
<td>0.05</td>
<td>5.8</td>
<td>-0.3</td>
<td>0.08</td>
<td>4.8</td>
</tr>
<tr>
<td>3</td>
<td>4.6</td>
<td>-0.20</td>
<td>7.6</td>
<td>3.1</td>
<td>-0.25</td>
<td>0.9</td>
</tr>
<tr>
<td>4</td>
<td>0.1</td>
<td>0.06</td>
<td>8.7</td>
<td>-0.3</td>
<td>0.11</td>
<td>3.2</td>
</tr>
<tr>
<td>5</td>
<td>-0.8</td>
<td>0.02</td>
<td>11.9</td>
<td>0.5</td>
<td>0.01</td>
<td>5.9</td>
</tr>
<tr>
<td>6</td>
<td>-0.6</td>
<td>0.09</td>
<td>2.7</td>
<td>-1.0</td>
<td>0.11</td>
<td>3.1</td>
</tr>
<tr>
<td>7</td>
<td>-0.8</td>
<td>0.16</td>
<td>2.4</td>
<td>-0.6</td>
<td>0.32</td>
<td>0.7</td>
</tr>
<tr>
<td>8</td>
<td>-0.6</td>
<td>0.27</td>
<td>1.1</td>
<td>-1.3</td>
<td>0.37</td>
<td>0.2</td>
</tr>
<tr>
<td>9</td>
<td>-0.5</td>
<td>0.05</td>
<td>5.0</td>
<td>-0.3</td>
<td>0.03</td>
<td>4.7</td>
</tr>
<tr>
<td>Mean</td>
<td>-0.1</td>
<td>0.05</td>
<td>6.2</td>
<td>0.0</td>
<td>0.09</td>
<td>3.3*</td>
</tr>
<tr>
<td>± 1 SD</td>
<td>1.7</td>
<td>0.13</td>
<td>6.2</td>
<td>1.3</td>
<td>0.18</td>
<td>2.3</td>
</tr>
</tbody>
</table>

(∗p < 0.05)

before E-643 administration was 36.8 ± 3.5 Torr, later falling to 35.1 ± 4.4 Torr during hypoxia. The decline in PaCO₂ was only 1.7 ± 1.4 Torr during, but it was found to be significant (p < 0.01) (Fig. 3). The pH during room air ventilation was 7.390 ± 0.021 and 7.420 ± 0.023 during hypoxic ventilation. The mean increase in the pH was 0.030 ± 0.017 (p < 0.001) (Fig. 4). These changes in blood gas data were almost the same before and during the 90 sec hypoxic stimulations after E-643 administration. Mean PaO₂ during room air ventilation after E-643 administration was 100.4 ± 13.7 Torr, while that during 5% O₂ was 35.8 ± 3.8 Torr. PaO₂ decreased by 64.6 ± 11.0 Torr (p < 0.001) (Fig. 2). Mean PaCO₂ decreased from the room air ventilation value of 35.6 ± 4.3 Torr to 33.2 ± 3.8 Torr after 90 sec of hypoxia. The difference of 2.4 ± 2.5 Torr was significant (p < 0.05) (Fig. 3). The pH increased by 0.031 ± 0.012

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(p < 0.001) during hypoxia (from 7.370 ± 0.040 to 7.401 ± 0.047) (Fig. 4). The changes in
PaCO₂ and pH were small and both were within
normal physiological ranges. There were no
significant differences in PaCO₂ and pH between
before and after the administration of E-643
during room air ventilation.

2. Changes in hemodynamic data
The control SAm value of 96.0 ± 19.3 mmHg
increased by 14.5 ± 14.2 mmHg to 110.6 ± 19.8
mmHg (p < 0.05) at the end of 90 sec of venti-
lation with 5% O₂. After E-643 administration,
SAm decreased to 88.0 ± 15.4 mmHg (p < 0.001).
The mean decrease was 8.0 ± 11.9
mmHg. At the end of 90 sec hypoxic stimulation
after E-643 administration, SAm increased from
a control value of 88.0 ± 15.4 mmHg to 95.3 ±
17.4 mmHg (7.3 ± 14.5 mmHg increase). This
change, however, was not significant (Fig. 5).
Before the administration of E-643, PAm
during room air ventilation was 18.5 ± 5.8 mmHg,
increasing to 24.9 ± 8.3 mmHg at the end of
hypoxia (increase of 6.4 ± 3.3 mmHg, p < 0.001).
After E-643 administration, the mean increase in
PAm (ΔPAm) was 3.9 ± 1.7 mmHg. This was significantly less than the value before
E-643 (p < 0.05) (Table I).

LAm and CO did not change significantly
during the study. PVR increased to 6.2 ± 3.8
HRU (p < 0.01) before E-643 administration
and increased to 3.3 ± 2.3 HRU (p < 0.01) after
E-643 administration. The increase in PVR
(ΔPVR) decreased by 3.0 ± 2.8 HRU (p < 0.05)
after the administration of E-643 (Table II).

DISCUSSION
Recently, selective α₁-adrenoceptor an-
tagons have been introduced as a therapy for
essential hypertension.11,12 It is said that α₁-
blockers reduce arterial blood pressure by sup-
pressing the contraction of vascular smooth muscle
mediated by post synaptic α₁-receptors, and
that they have little or no affinity for presynaptic
α₁-adrenoceptors13–15 The enervation of the
pulmonary blood vessels is partly para-
sympathetic via the vagus and partly sympa-
thetic.16 It is believed that these nerves have little
direct relation to the dilatation or constriction of
the pulmonary blood vessels17,18 However, in-
creasing pulmonary arterial blood pressure by the
administration of α₁-stimulators, or increasing
cardiac output by the stimulation of sympathetic
nerves during whole lung hypoxia8,19,20 have
demonstrated the contribution of the sympa-
thetic nerves.

Since the pulmonary circulation operates
at low pressure compared to the systemic circu-
lation, it is easily altered by the hydrostatic,
lung interstitial and pulmonary alveolar pressures.
The lung volume and recruitment of the pulmo-
nary vasculature should be taken into account
when evaluating the effects of drugs on the
pulmonary vasculature.21 However, it is not easy
to evaluate the effects of drugs on the
pulmonary circulation. No selective pulmonary
vasodilators are available and no drug which
has been established to be effective at producing
pulmonary vasodilation without nitroglycerin
co-administration exists. Nitroglycerin is only
slightly effective at decreasing systemic blood
pressure, and it is not an ideal pulmonary vaso-
dilator because it causes hypoxemia due to venti-
lation/perfusion mismatch in the lung22 Clin-
ically, the drug that is the best therapy for the
particular pulmonary hypertensive disease is
selected.

Alpha-blockade with phentolamine lowers
pulmonary vascular resistance slightly, suggesting
either spontaneous activity of the alpha-receptor
mechanism, or an effective level of a circulating
α₁-agonist, such as norepinephrine, or even
an agent such as histamine, whose constrictor
action is greatly influenced by alpha-blockade.23
α₁-blockers do not activate the release of
norepinephrine by blocking α₂-receptors.14
However, they may be effective for hypoxic
pulmonary vasoconstriction, so we evaluated the
effects of E-643, a selective α₁-blocker, on
acute HPV in mongrel dogs.

In this experiment, 5% O₂ inhalation for
90 sec was thought to be a sufficient hypoxic
stimulation to bring about pulmonary vaso-
constriction. The dose of E-643 was not fixed.
The effects on the pulmonary vasoconstriction
were evaluated at the point of maximal decrease
in PVR (within a 20% decrease in SAm), because
E-643 is known as an anti-hypertensive drug
which does not only affect pulmonary hyper-
tension without causing systemic effects. Clin-
ically, pulmonary arterial pressure depression is
accompanied by a far greater decrease in systemic
pressure, and harmful effects have been observed
with hydralazine therapy for pulmonary hyper-
tension23,24

Prior to E-643 administration, PAm increased
by an average of 6.4 mmHg at the end of 90 sec.
of 5% O2 induced hypoxia (p < 0.001) and PVR also increased significantly (p < 0.001). After administration of E-643, ΔPAm decreased significantly (p < 0.05) without decreasing cardiac output. This illustrates the vasodilating effects of E-643 on the hypoxic pulmonary hypertension. A fall in PaO2, reported after sublingual nitroglycerin, was not observed in this experiment. This suggests that E-643 administration in this method does not increase the ventilation/perfusion unevenness in the lung.

After the administration of E-643, the increase in PAm and PVR by 5% hypoxic ventilation were slightly reduced. In this experiment, several 90 sec hypoxic stimulations with 5% O2 were carried out. Such repetitive hypoxic stimulations have been found to increase pulmonary artery hypoxic vasoconstrictions. However, even when the HPV increased due to the repetitions, the vasodilating effects of E-643 on HPV are not overestimated because the maximal PAm and PVR during hypoxia after administration of E-643 decreased.

A slight decrease in PaCO2 and a slight increase in pH were observed during each 90 sec 5% hypoxia. These may be due to the Haldane effect brought about by hypoxemia. It is thought that hypercapnea and acidosis strengthen the HPV, while hypocapnea and alkalosis reduce HPV. In the present study hypocapnea and alkalosis reduced the response to the pulmonary artery hypoxia. However, the levels of hypocapnea and alkalosis, before and after E-643 administration did not differ. The changes in these factors were small and within normal physiological limits, so they are not responsible for the effects of E-643 on HPV.

It is believed that HPV occurs not only via sympathetic nerves because HPV was observed after the resection of sympathetic nerves and in isolated perfused lungs. The reduction in HPV after E-643 administration illustrates the effectiveness of alpha1-blockers on HPV. HPV may be partially due to sympathetic activity, similar to alpha-blocker depression of pulmonary hypertension after the administration of oral phentolamine. Alpha1-blockers may be more appropriate for treating HPV than non-selective alpha-blockers because they do not enhance the release of noradrenaline following a loss of the feedback inhibitory mechanisms mediated by pre-synaptic alpha-receptors.

In summary, the fact that the alpha1-blocker, E-643, was observed to depress pulmonary hypertension due to hypoxic pulmonary vasoconstriction in dogs suggests the possibility of it being used for the treatment of human HPV caused by sleep apnea syndrome, or as a therapy for exercise-induced pulmonary hypertension in chronic obstructive lunging disease. The human lung, however, is different from the dog lung in terms of sympathetic response. So the appropriate clinical tests must first be carried out.

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