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Endothelin receptor blockade attenuates air embolization-induced pulmonary hypertension in sheep

Takashige Miyahara [a], Tomonobu Koizumi [a,*], Keishi Kubo [a], Masayuki Hanaoka [a], Toshimichi Kaneki [a], Hirashi Yamamoto [a], Ri-Li Ge [a], Keisaku Fujimoto [a], Toshio Kobayashi [a], Toshishige Shibamoto [b]

[a] *First Department of Internal Medicine, Shinshu University School of Medicine, 3-1-1, Asahi Matsumoto, 390-8621 Japan*
[b] *Department of Physiology, Division 2, Shinshu University School of Medicine, 3-1-1, Asahi Matsumoto, 390-8621, Japan*

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Abstract

We investigated the effects of two types of endothelin receptor antagonists on pulmonary hypertension induced by pulmonary air embolization in awake sheep. We prepared awake sheep with indwelling catheters inserted in blood vessels for continuous monitoring of pulmonary artery pressure, left atrial pressure and systemic arterial pressure. Cardiac output was measured every 30 min. The study consisted of two experiments, one with FR139317 (100 μg/kg/min; (*R*)2-[(*R*)-2-[(*S*)-2-[1-(hexahydro-1*H*-azepinyl)]-carbonyl]amino-4-methyl-pentanoyl]amino-3-[3-(1-methyl-1*H*-indolyl)]propionyl)amino-3-(2-pyridyl)propionic acid), a selective endothelin ET_A receptor antagonist, and the other with TAK-044 (100 μg/kg/h; cyclo[D-α-aspartyl-3-[(4-phenylpiperazin-yl)carbonyl]-L-alanyl-L-α- aspartyl-D-2-(2-thienyl) glycyl-L-leucyl-D-tryptophyl] disodium salt), an endothelin ET_A and ET_B receptor antagonist. In the paired experiments, air was continuously (4.06 ml/min) infused into the main pulmonary artery for 3 h after the baseline pressures were stabilized. Sheep were treated or not treated with FR139317 or TAK-044. Pulmonary artery pressure was significantly higher than the baseline pressure after the start of air infusion. Both FR139317 and TAK-044 significantly attenuated the increase in pulmonary artery pressure during air embolization. Plasma endothelin -1 levels in both pulmonary and systemic arteries were equally and significantly increased after the start of air infusion. The results indicate that endothelin-1 release is attributable to the development of pulmonary hypertension during the course of air embolization in awake sheep.

Keywords: Endothelin-1; Pulmonary embolization; Pulmonary vascular resistance; TAK-044; FR139317

1. Introduction

Endothelins are a group of potent vasoactive peptides composed of 21 amino acids. They are primarily produced by endothelial cells (Yanagisawa et al., 1988). Three isoforms of the peptides, endothelin-1, 2 and 3, have been identified as ETs that exhibit vasoconstrictor properties. Their potencies, however, are known to be different (Inoue et al., 1989; Barnes, 1994). Subsequent studies have revealed that ETs elicit various biological responses in pulmonary tissues (Gassin et al., 1991; Krzeski et al., 1991; Toga et al., 1992; Barnes, 1994; Barman and Pauly, 1995), and that endothelin receptors occur widely in the lung; i.e., in blood vessels, bronchi and alveoli (Koseki et al., 1989; Nakamichi et al., 1992; Goldie et al., 1996). In particular, endothelin-1 has various hemodynamic effects on the pulmonary circulation, including sustained vasoconstriction, vasorelaxation and a biphasic action (Gassin et al., 1991; Krzeski et al., 1991; Toga et al., 1992; Bonvallet et al., 1993). The responses of the pulmonary circulation to endothelin-1 may depend on species, age, experimental model and/or pulmonary vascular tone (Gassin et al., 1991; Krzeski et al., 1991). Recent studies have demonstrated an increased level of endothelin-1 in lung tissues and/or plasma samples in experimental animals (Li et al., 1994; Stelzner et al., 1992) as well as in humans with pulmonary hypertension (Goerre et al., 1995; Stewart et al., 1991). In addition, the recent development of several endothelin receptor antagonists has revealed the physio-

* Corresponding author. Tel.: +81-263-35-4600 (ex 5252); fax: +81-263-36-3722.

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logical role of endothelins in pulmonary vascular diseases (Bonvallet et al., 1993, 1994; Cardell et al., 1993). Treatment with endothelin receptor antagonists attenuated the pulmonary hypertension induced by chronic hypoxia (Bonvallet et al., 1994) or dehydromonocrotaline (Miyauchi et al., 1993; Okada et al., 1995a,b). The evidence from these studies implicates endothelins in the development of pulmonary hypertension.

Continuous intravenous infusion of air in conscious sheep caused pulmonary hypertension and increased pulmonary vascular permeability (Flick et al., 1983; Fukushima and Kobayashi, 1986; Pou et al., 1993; Miyahara et al., 1996). There is little information about the chemical and/or hormonal contribution to the development of pulmonary hypertension during air embolization. The present study was conducted to assess the role of endothelin-1 in pulmonary hypertension. We tested the effects of two different endothelin receptor antagonists on the pulmonary hypertension induced by air embolization in sheep.

2. Methods

2.1. Animal preparation

We prepared yearling sheep (weighing 25–40 kg) for continuous pressure monitoring in the manner previously reported by our colleagues (Fukushima and Kobayashi, 1986; Miyahara et al., 1996). In brief, each animal was intubated under anesthesia with intravenous pentobarbital sodium (12.5 mg/kg). Ventilation was maintained with 0.5–1.0% halothane. Left thoracotomy was performed under sterile conditions. Silicon catheters were directly inserted into the main pulmonary artery and the left atrium. A thin silicone tube (0.6 mm internal diameter and 1.2 mm outer diameter) was inserted into the main pulmonary artery for infusion of air. A catheter was placed through the right neck incision into the thoracic aorta and an 8-Fr catheter sheath introducer (Cordis Labo, Miami, FL) was passed into the superior vena cava. The experiment was done at least 6 days after surgery when the animal had fully recovered.

2.2. Measurements

Mean pulmonary arterial pressure, left atrial pressure and systemic arterial pressure were continuously recorded. Cardiac output was measured by thermodilution method. Endothelin-1 levels in the systemic and pulmonary arteries were determined by radioimmunoassay (Ando et al., 1989). Blood samples were drawn from the left atrium and pulmonary artery at baseline, 1.5, 3.0 and 4.0 h after the start of air infusion. Blood gas analysis was performed simultaneously. Pulmonary vascular resistance was calculated by determining (pulmonary artery pressure–left atrial pressure)/cardiac output.

2.3. Agents

FR139317, ((*R*)2-[(*R*)-2-[(*S*)-2-[1-(hexahydro-1*H*-azepinyl)]-carbonyl]amino-4-methyl-pentanoyl]amino-3-[3-(1-methyl-1*H*-indolyl)]propionyl)amino-3-(2-pyridyl)propionic acid), an ET_A receptor antagonist, kindly provided by Fujisawa Pharmaceutical, Osaka, Japan.

FR139317 competitively antagonizes the endothelin-1 and -2-induced contractions of several animal vessels (Cardell et al., 1993; Okada et al., 1995a,b). TAK-044, cyclo[D-α-aspartyl-3-[(4-phenylpiperazin-yl)carbonyl]-L-alanyl-L-α- aspartyl-D-2-(2-thienyl) glycyl-L-leucyl-D-tryptophyl] disodium salt, is an endothelin receptor antagonist that shows potent inhibitory effects on both endothelin ET_A and ET_B-mediated responses (Ikeda et al., 1993; Kusumoto et al., 1994). The drug was kindly supplied by Takeda Chemical Industries, Osaka, Japan. FR139317 and TAK-044 were dissolved in normal saline. Each solution was prepared within 30 min in the experiments to avoid any possible degradation.

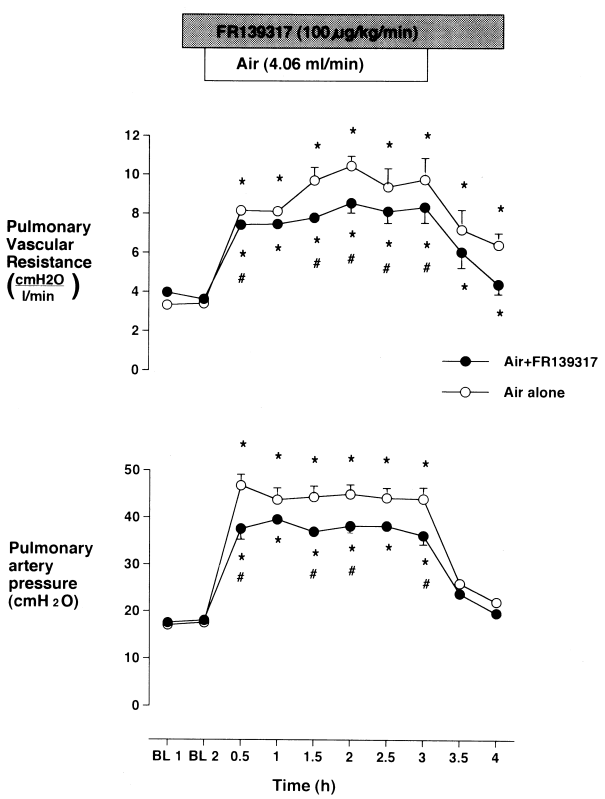

Fig. 1. Time courses of pulmonary artery pressure and pulmonary vascular resistance after air embolization in sheep with and without FR139317. FR139317; a selective endothelin ET_A receptor antagonist. BL1: baseline before FR139317 infusion; BL2: baseline before air infusion. ★: significant difference from baseline 1 and 2; #: significant difference between with and without FR139317.

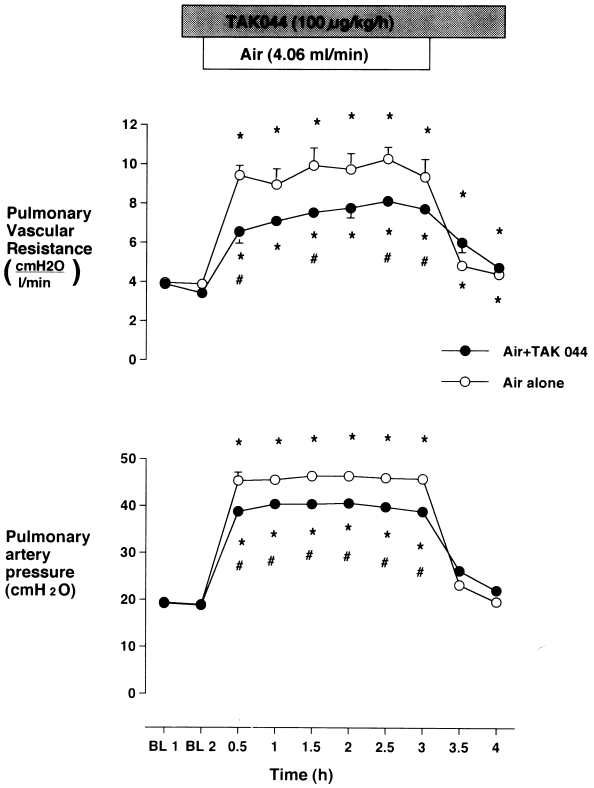

Fig. 2. Time courses of pulmonary artery pressure and pulmonary vascular resistance after air embolization in sheep with and without TAK-044. TAK-044; an endothelin ET_A and ET_B receptor antagonist. BL1; baseline before TAK-044 infusion, BL2; baseline before air infusion. ★: significant difference from baseline 1 and 2; #: significant difference between with and without TAK-044.

2.4. Experimental protocol

Experiments were performed with awake animal in the standing position. Two experiments were done in the present study. Experiment 1 ($n = 5$): The animals were treated or not treated with FR139317 during air embolization. As control, normal saline (60 ml/h) was started after the baseline values were stabilized over 2 h. Thirty minutes (min) after infusion of normal saline, air was continuously infused (4.06 ml/min) through the thin tube, using a constant rate infusion pump, for 3 h. Administration of FR139317 (100 μg/kg/min, 60 ml/h) was started at the time of administration of normal saline in the control experiment and continued for 4 h after starting air infusion. Experiment 2 ($n = 5$): The animals were treated or not treated with TAK-044 during air embolization. Air and normal saline were continuously infused in the same manner as for the control in Experiment 1. Infusion of TAK-044 (100 μg/kg/h, 60 ml/h) was started 30 min before air infusion, and continued for 4 h. A paired study was conducted in each experiment. The experimental agent was administered in randomized order.

2.5. Statistical evaluation

Values shown in the table and figures are presented as means ± S.E. Data were analyzed by Dunnett's multiple comparison test, and differences were tested using Friedman test. A P value of less than 0.05 was considered statistically significant.

3. Results

3.1. Pulmonary hemodynamics

The time courses of pulmonary hemodynamic parameters are summarized in Figs. 1 and 2 and Tables 1 and 2. In both experiments, neither endothelin-receptor antagonists nor normal vehicle affectted the pulmonary hemodynamics before air infusion. In Experiment 1, pulmonary artery pressure rose significantly from 17.0 ± 1.1 cmH_2O

Table 1
Effects of air embolism on the pulmonary hemodynamics with and without FR139317 treatment in awake sheep
Values are means ± S.E. BL1; baseline without drug and/or normal saline. BL 2; new baseline after the start of drug infusion and/or normal saline. PA; mean pulmonary artery pressure (cmH_2O), LA; mean left atrial pressure (cmH_2O), CO; cardiac output (l/min), PVR; pulmonary vascular resistance (cmH_2O/l/min). FR139317; a selective endothelin ET_A receptor antagonist.

Experiment 1 ($n = 5$)	BL1	BL 2	0.5 h	1 h	2 h	3 h	4 h
Control							
PA	17.0 ± 1.1	17.5 ± 1.2	46.8 ± 2.3[a]	43.8 ± 2.3[a]	45.0 ± 1.8[a]	44.0 ± 2.4[a]	22.0 ± 1.2
LA	2.0 ± 0.9	2.2 ± 0.7	3.8 ± 0.5	3.1 ± 0.5	2.3 ± 0.5	1.8 ± 0.6	0.6 ± 0.6
CO	4.6 ± 0.3	4.6 ± 0.3	5.2 ± 0.4	5.0 ± 0.5	4.2 ± 0.4	4.7 ± 0.4	3.6 ± 0.2
PVR	3.3 ± 0.2	3.4 ± 0.2	8.2 ± 0.3[a]	8.1 ± 0.3[a]	10.4 ± 0.5[a]	9.8 ± 0.9[a]	6.4 ± 0.5
FR139317							
PA	17.5 ± 0.4	18.0 ± 0.6	37.6 ± 2.1[a,b]	39.6 ± 1.6[a,b]	38.2 ± 1.5[a,b]	36.2 ± 1.7[a,b]	19.6 ± 0.6
LA	1.4 ± 0.7	1.3 ± 0.7	1.4 ± 0.7	2.3 ± 0.9	0.1 ± 1.0	−0.5 ± 1.6	−0.7 ± 1.7
CO	4.2 ± 0.3	4.7 ± 0.2	5.0 ± 0.3	5.0 ± 0.2	4.5 ± 0.2	4.5 ± 0.3	4.7 ± 0.1
PVR	4.0 ± 0.4	3.6 ± 0.3	7.4 ± 0.4[a,b]	7.5 ± 0.4[a,b]	8.6 ± 0.4[a,b]	8.3 ± 0.8[a,b]	4.4 ± 0.5

[a] $P < 0.05$ vs. baseline 1 and 2.
[b] $P < 0.05$ vs. control.

Table 2
Effects of air embolism on the pulmonary hemodynamics with and without TAK-044 treatment in awake sheep
Values are means ± S.E. BL1; baseline without drug and/or normal saline. BL 2; new baseline after the start of drug infusion and/or normal saline. PA; mean pulmonary artery pressure (cmH_2O), LA; mean left atrial pressure (cmH_2O), CO; cardiac output (l/min), PVR; pulmonary vascular resistance (cmH_2O/l/min). TAK-044; an endothelin ET_A and ET_B receptor antagonist.

Experiment 2 ($n = 5$)	BL1	BL 2	0.5 h	1 h	2 h	3 h	4 h
Control							
PA	19.4 ± 0.9	18.9 ± 0.9	45.4 ± 1.7[a]	45.6 ± 0.6[a]	46.4 ± 1.1[a]	45.8 ± 1.0[a]	19.6 ± 0.8
LA	1.1 ± 0.5	1.2 ± 0.5	1.8 ± 0.5	0.8 ± 0.9	0.2 ± 0.8	0.7 ± 0.7	0.0 ± 1.1
CO	4.7 ± 0.2	4.6 ± 0.2	4.7 ± 0.4	5.2 ± 0.3	4.9 ± 0.4	5.0 ± 0.3	4.7 ± 0.4
PVR	3.9 ± 0.3	3.9 ± 0.3	9.4 ± 0.5[a]	8.9 ± 0.7[a]	9.7 ± 0.8[a]	9.3 ± 0.9[a]	4.4 ± 0.4
TAK-044							
PA	19.2 ± 0.7	18.8 ± 0.6	38.8 ± 1.1[a,b]	40.4 ± 0.9[a,b]	40.6 ± 0.9[a,b]	38.8 ± 0.6[a,b]	22.0 ± 1.0
LA	1.1 ± 0.3	1.4 ± 0.6	2.8 ± 1.2	2.2 ± 1.1	2.0 ± 1.0	0.6 ± 0.8	0.0 ± 0.6
CO	4.7 ± 0.1	5.1 ± 0.1	5.6 ± 0.2	5.4 ± 0.2	5.1 ± 0.3	5.0 ± 0.2	4.6 ± 0.1
PVR	3.9 ± 0.3	3.4 ± 0.3	6.5 ± 0.4[a,b]	7.1 ± 0.4[a,b]	7.8 ± 0.5[a,b]	7.7 ± 0.4[a,b]	4.7 ± 0.3

[a] $P < 0.05$ vs. baseline 1 and 2.
[b] $P < 0.05$ vs. control.

at baseline to 46.8 ± 2.3 cmH_2O 0.5 h after beginning air infusion. Pulmonary artery pressure remained stable during air infusion and returned to its baseline value within 1 h after the cessation of air infusion. Left atrial pressure and cardiac output did not change significantly during the experiment. Thus, pulmonary vascular resistance showed a significant increase during air infusion. In the group treated with FR139317, pulmonary artery pressure rose from 17.5 ± 0.4 cmH_2O at baseline to 37.6 ± 2.1 cmH_2O during air infusion. No significant differences were observed in the time courses of left atrial pressure and cardiac output values. Thus, the increases in pulmonary artery pressure and pulmonary vascular resistance with FR139317 were significantly less than those with air infusion alone. In Experiment 2, the time courses of pulmonary hemodynamics after air infusion were similar to those in Experiment 1. TAK-044 attenuated the increased pulmonary artery pressure and pulmonary vascular resistance induced by air infusion (Fig. 2 and Table 2). There were no significant differences in the decrease of pulmonary artery pressure and pulmonary vascular resistance between the animals treated with FR139317 and those with TAK-044.

Table 3
Analysis of partial oxygen tension during air embolism in awake sheep
Values are means ± S.E. (Torr). BL: baseline, FR139317: a selective endothelin ET_A receptor antagonist, TAK-044: an endothelin ET_A and ET_B receptor antagonist.

Time	BL	1.5 h	3 h	4 h
Experiment 1 (n = 5)				
Control	82.5 ± 2.2	60.9 ± 3.5[a]	53.4 ± 3.5[a]	66.1 ± 4.1[a]
FR139137	82.5 ± 2.5	57.6 ± 3.5[a]	63.2 ± 5.0[a]	70.7 ± 3.7[a]
Experiment 2 (n = 5)				
Control	84.5 ± 1.5	55.4 ± 2.6[a]	60.7 ± 3.4[a]	73.4 ± 2.2
TAK-044	84.3 ± 2.0	58.7 ± 4.1[a]	54.6 ± 3.5[a]	71.8 ± 2.4

[a] $P < 0.05$ vs. baseline.

3.2. Arterial blood gas analysis

During air infusion, all sheep developed rapid, shallow and labored breathing. In both experiments, partial oxygen tension (P_aO_2) significantly fell during air infusion (Table 3). There were no significant differences between the animals treated with air alone and the drug-treated animals. After cessation of air infusion, P_aO_2 did not return to the baseline value despite the improvement of pulmonary hemodynamics. There were no significant differences in pH and PCO_2 during air embolism.

3.3. Endothelin-1 levels

The plasma endothelin-1 levels are shown in Table 4. The endothelin-1 levels in pulmonary artery and left atrium increased significantly after the start of air infusion. The increase of endothelin-1 levels in pulmonary artery and left

Table 4
Effects of air embolism on plasma concentration of ET-1 in pulmonary artery and left atrium with and without drug treatment in awake sheep
Values are means ± S.E. (pg/ml) BL; baseline, FR139317; endothelin ET_A receptor antagonist, TAK-044; endothelin ET_A and ET_B receptor antagonist.

Experiment 1 ($n = 5$)	Time	BL	1.5 h	3 h	4 h
Pulmonary	Control	4.8 ± 0.4	7.0 ± 1.2[a]	9.0 ± 1.4[a]	11.0 ± 1.4[a]
artery	FR139317	5.4 ± 0.5	9.2 ± 0.8[a]	10.4 ± 1.2[a]	11.5 ± 1.5[a]
Left atrium	Control	4.8 ± 0.5	7.4 ± 1.1	8.8 ± 1.1[a]	10.4 ± 1.3[a]
	FR139317	5.1 ± 0.3	8.1 ± 0.7[a]	9.5 ± 0.8[a]	11.3 ± 1.7[a]
Experiment 2 (n = 5)					
Pulmonary	Control	6.0 ± 0.6	8.5 ± 1.1	9.5 ± 1.5[a]	8.9 ± 0.7[a]
artery	TAK-044	4.8 ± 0.5	6.3 ± 0.6[a]	7.3 ± 0.6[a]	8.4 ± 0.6[a]
Left atrium	Control	5.6 ± 0.6	7.3 ± 1.1[a]	9.6 ± 1.2[a]	9.6 ± 0.4[a]
	TAK-044	5.3 ± 0.5	6.4 ± 0.4	7.6 ± 0.8[a]	7.9 ± 0.8[a]

[a] $P < 0.05$ vs. baseline.

atrium were almost the same, with no significant differences.

4. Discussion

In the sheep model of pulmonary air embolization, pulmonary artery pressure promptly increased after the start of air infusion, and remained stable during infusion of air at a constant rate. Pulmonary artery pressure then returned to its baseline value within 0.5–1.0 h after cessation of air infusion (Flick et al., 1983; Fukushima and Kobayashi, 1986; Pou et al., 1993; Miyahara et al., 1996). Furthermore, a previous study in our laboratory had shown that the increase in pulmonary artery pressure was independent of the thromboxane-release pathway (Fukushima and Kobayashi, 1986). Thus, it has been thought that the major cause of pulmonary hypertension is the direct vascular obstruction by air bubbles. Hormonal factors seem to be less involved in the mechanism of air embolization-induced pulmonary hypertension. In the present study, however, we found that plasma endothelin-1 levels were higher during pulmonary air embolization, and that both selective endothelin ET_A and combined endothelin ET_A and ET_B receptor antagonists attenuated the increased pulmonary artery pressure and pulmonary vascular resistance during pulmonary air embolization. Although the attenuation by endothelin receptor antagonists was slight, the data indicated that endothelin-1 was partly involved in the pulmonary hypertension induced by air embolization in sheep.

Endothelins have a potent vasoactivity and play an important role in regulating pulmonary vascular tone (Cassin et al., 1991; Toga et al., 1992; Barnes, 1994; Barman and Pauly, 1995). The pharmacological responses to endothelins are mediated by at least two receptor subtypes, endothelin ET_A and ET_B (Barnes, 1994). The role of these receptors remains controversial. The actions exerted via these receptors show tone-dependent responses in some animals (Cassin et al., 1991; Krzeski et al., 1991). In general, however, endothelin ET_A receptor is relatively selective for endothelin-1, and mediates the vasoconstrictive effect of endothelins. On the other hand, endothelin ET_B receptor has equal affinity to endothelins. It is mainly located on endothelial cells (Barnes, 1994). The dominant effect of the endothelin ET_B receptor may be vasorelaxation (Wong et al., 1995). However, the distribution and binding affinity of both endothelin ET_A and ET_B vary with the sizes of pulmonary vessels, though both receptor subtypes coexist in the pulmonary vascular muscle (Bonvallet et al., 1993; Barman and Pauly, 1995). In the present study, we failed to find any physiological differences in the endothelin ET_A and ET_B effects during pulmonary air embolization. This, however, was not a goal of the present study. Since there were no significant differences in the decrease of the air embolization-induced pulmonary hypertension between the FR139316 and TAK-044 treatment groups, it is possible that an obvious endothelin ET_B receptor blocking effect with TAK-044 was not achieved in the present study. Okada et al. (1995a) showed that injection of an endothelin ET_B receptor antagonist increased pulmonary vascular tone in the 8th week of dehydromonocrotaline-induced pulmonary hypertension. Furthermore, the pulmonary vasodilation responses to endothelin-1 injection were not attenuated by the endothelin ET_A receptor antagonist but were by the endothelin ET_B receptor antagonist when pulmonary hypertension was well established (8th week after dehydromonocrotaline). The authors suggested that the vasoresponse via the endothelin ET_B receptor was dominant in the pulmonary hypertension induced by dehydromonocrotaline. It was shown, however, that continuous treatment with an endothelin ET_B receptor antagonist did not affect the degree of pulmonary hypertensive vascular tone induced by monocrotaline in beagles (Okada et al., 1995b). Thus, activation of endothelin ET_A and ET_B receptors is complex and may depend on the time courses and degree of pulmonary hypertension. Although it was possible that the endothelin ET_B receptor was activated in the present study, the physiological action exerted through endothelin ET_B receptors was minor compared to the constrictive effect of ET_A receptors.

An endothelin ET_A receptor antagonist attenuated the pulmonary hypertension induced by chronic hypoxia (Bonvallet et al., 1994) as well as by monocrotaline (Miyauchi et al., 1993; Okada et al., 1995a,b). These studies were done with a chronic experimental design. Since endothelin-1 has been shown to stimulate the proliferation of vascular smooth muscle and fibroblasts (Muldoon et al., 1989; Takuwa et al., 1989), endothelins regulate pulmonary vascular remodeling during the course of development of pulmonary hypertension. Prolonged and continuous air embolization in sheep causes functional and structural changes in the pulmonary artery (Perkett et al., 1991) which were not observed in an acute study. Although we found in the present study that endothelin-1 was involved in the acute air embolization, it would be interesting to investigate the role of endothelins in the functional and structural changes of continuous air embolization.

In the present study, we were unable to identify the source of the increased endothelin-1 during air embolization. There was no significant gradient in endothelin-1 levels between left atrium and pulmonary artery. Lung is known to be the primary site of extraction for endothelin-1 (De Nucci et al., 1988; Sirvio et al., 1990). Goerre et al. (1995) demonstrated that arterial endothelin-1 levels were lower than venous endothelin-1 levels in healthy volunteers living at a high altitude. In contrast, Stewart et al. (1991) reported that the arterial endothelin-1 levels were persistently greater than the venous levels in patients with primary pulmonary hypertension. Thus, the clearance and/or production of endothelin-1 in the lung might differ according to the pulmonary vascular status. As there were no significant differences in the systemic pressure during

air infusion, we presumed that shear stress caused by air obstruction in the precapillary bed stimulated the endothelium to release endothelin-1.

Several investigators have shown that in the air embolization sheep model, a protein-rich and increased lung lymph flow was observed after recovery of the pulmonary hemodynamics, suggesting an increased pulmonary microvascular permeability (Flick et al., 1983; Fukushima and Kobayashi, 1986; Pou et al., 1993; Miyahara et al., 1996). The mechanism remains unknown. We succeeded with the measurement of the lung lymph flow in two animals of Experiment 2. We found a modest increase in lung lymph flow in the endothelin receptor antagonist treatment groups (control: from 1.5 ± 1.0 ml/15 min at baseline to 6.2 ± 1.8 at 4 h after starting air infusion; TAK-044 treatment: 1.6 ± 0.6 ml/15 min at baseline to 4.5 ± 1.8 at 4 h after start of air infusion). The increased plasma endothelin-1 level even after cessation of air infusion suggests that endothelin-1 may relate to the development of air embolism-induced lung injury. Mizutami et al. (1998) found in a canine lung transplantation model that TAK-044 attenuated ischemic-reperfusion injury. Thus, it is likely that endothelins play an important role in several pathophysiological conditions. It has been shown that in adult sheep pulmonary veins are more sensitive than arteries to endothelins (Toga et al., 1992). An increase in venous resistance induced by endothelin release may contribute to transvascular fluid filtration and/or edema formation during air embolization, although air obstruction occurred in the precapillary pulmonary vascular bed.

In summary, the present study demonstrated that endothelin receptor activation occurred during pulmonary air embolization and that endothelin receptor antagonists (FR 139317 and TAK-044) attenuated the pulmonary pressor response to air embolization in sheep. Endothelin-1 release was a hormonal involvement in the pathophysiology of pulmonary hypertension induced by air embolization in sheep, although its contribution was only slight. Furthermore, FR139317 and TAK-044 were considered to be useful for evaluation of the role of ETs in various pathophysiological conditions.

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