Acta Med. Nagasaki 44 : 55–60

Adrenomedullin is not Related to Acute Hypoxic Pulmonary Vascular Response in Patients with Chronic Respiratory Disease

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In the present study, acute hypoxia was induced in 19 patients with chronic respiratory disease to evaluate the corre lation between pulmonary circulation kinetics and adrenomedullin (AM) levels. Using radioimmunoassay (RIA), pulmonary circulation kinetics were evaluated before and after hypoxic loading (13% oxygen for 15 minutes) by determining AM levels in plasma obtained from the pulmonary artery (PA) and the right femoral artery (FA). There were no significant differences in pre-hypoxia plasma AM levels between samples obtained from the PA and FA, and plasma AM levels did not change after hypoxic loading. Subjects were classified into two groups [responders (R) and non-responders (NR)] to evaluate changes in the mean pulmonary arterial pressure (ΔMPAP). There were no changes in AM levels between these two groups in either the PA or FA after hypoxic loading. These results suggest that AM do not appear to be related to hypoxic pulmonary vascular response to acute hypoxic loading in patients with chronic respiratory disease.

Key words: human adrenomedullin, hypoxic pulmonary vaso constriction, acute hypoxia

Introduction

In 1946, Von Euler and Liljestrand first reported that pulmonary vascular constriction was induced by a rapid decrease in alveolar oxygen levels, resulting in increased pulmonary arterial pressure.[1] This phenomenon was referred to thereafter as hypoxic pulmonary vasoconstriction (HPV), and several studies have been conducted.[2-4] However, the mechanism of HPV remains to be clarified.

Adrenomedullin (AM) is a newly-identified vasodilative peptide isolated from human pheochromocytoma tissues.[5] Markedly potent human AM mRNA expression has been observed in pheochromocytoma tissue and the adrenal medulla as well as in the lung[6]. Specific receptors for AM have been reported in cultured rat vascular endothelial cells (EC) as well as in vascular smooth muscle cells (VSMC).[7] The vasodilative action of AM is considered to result from nitric oxide (NO) production in EC and increased cAMP levels in VSMC.[8] The level of AM receptors is reportedly high in the rat lung.[9] Moreover, plasma AM levels are significantly low in the right heart circulatory system compare to that in the left.[10] Thus, the pulmonary circulation may intrinsically involve in plasma AM clearance.

To evaluate the pathophysiological significance of AM, hypoxia was induced in patients with chronic respiratory disease, and pulmonary circulation kinetics were determined together with plasma AM levels before and after hypoxic loading.

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Subjects and Methods

Subjects

Subjects consisted of 19 patients with chronic respiratory disease (8 men and 11 women). Cases included pulmonary emphysema (n=6), diffuse panbronchiolitis (n=2), pulmonary tuberculosis sequela (n=2), atypical mycobacteriosis (n=4), pulmonary fibrosis (n=1), pulmonary aspergilloma (n=2) and collagen disease of the lung (n=2). Diagnoses were based on physical examinations, hematological examination, chest roentgenography, computed tomography, pulmonary function test, transbronchial lung biopsy and open lung biopsy. Examinations were performed in each patient during clinically stable phases of the disease course. Table 1

shows patient ages and findings on arterial blood gas analysis, while Table 2 shows findings on pulmonary function test. Informed consent was obtained from all patients.

Table 1. Patient characteristics (n=19).

Age (years)	65 ± 7
$PaCO_2$ (Torr)	41.1 ± 4.7
PaO_2 (Torr)	86.5 ± 13.9
PvO_2 (Torr)	42.3 ± 8.4
pH	7.417 ± 0.03

Values are means±SD. $PaCO_2$: arterial carbon dioxide tension, PaO_2: arterial oxygen tension, PvO_2: pulmonary arterial oxygen tension.

Table 2. Pulmonary function tests of all subjects.

atient No.	Diagnosis	FEV_1/FVC(%)	VC(%predicted)	DLCO(%predicted)
1	PE	54.8	50.6	58.8
2	AM	85.2	93.6	72.1
3	PE	85.2	58.6	96.8
4	PE	59.0	97.0	88.5
5	AM	69.5	102.0	84.8
6	CL	70.0	45.8	72.6
7	AM	86.1	51.5	52.4
8	PT	94.2	104.3	109.1
9	DPB	64.5	115.8	88.5
10	AM	79.3	45.7	122.0
11	PE	79.9	124.6	73.0
12	PE	60.4	101.7	70.8
13	PA	57.1	84.6	83.5
14	PA	84.6	78.9	67.1
15	PT	84.8	79.8	72.8
16	CL	72.8	57.4	27.0
17	PF	94.6	79.4	49.7
18	DPB	82.7	67.2	64.7
19	PE	78.8	77.1	28.2
		25.8		

PE: pulmonary emphysema, AM: atypical mycobacterosis, CL: collagen disease of the lung, PT: pulmonary tuberculosis sequela, DPB: diffuse panbronchiolitis, PA: pulmonary aspergilloma, PF: pulmonary fibrosis, FEV_1/FVC: forced vital capacity expired in 1s, VC: vital capacity, DLCO: carbon monoxide diffusing capacity.

Methods

Administration of drugs that influence circulation kinetics or the central nervous system was discontinued on the day before examination. All examinations were performed on fasting patients without premedication. Right heart catheterization was performed using a Swan-Ganz catheter (model TF002H-7F, Baxter Healthcare) via the right femoral vein with patients in the supine resting position to determine pulmonary capillary wedge pressure (PCWP), mean pulmonary arterial pressure (MPAP), and mean right atrial pressure (MRAP). Cardiac output (CO) was determined by the thermodilution method, using REF-1 ejection fraction/CO computer (Edwards Critical Care Division). Body surface area (BSA) was calculated according to the by DuBois formula,[11] and cardiac index (CI) was obtained by the following equation based on the CO and BSA values: $CI = CO/BSA\ (l/min/m^2)$

Total pulmonary vascular resistance (TPR) and pulmonary vascular resistance (PVR) were calculated according to the following equations: $TPR = MPAP/CO \times 80$ (dyne·sec·cm^{-5}). $PVR = (MPAP - PCWP)/CO \times 80$ (dyne·sec·cm^{-5}).

A 20G catheter (Arterial Line Kit, USA) was inserted via the right femoral artery (FA) to determine the mean arterial pressure (MAP) as well as to collect blood samples. Blood samples were also collected from the pulmonary artery (PA) for AM level determination and blood gas analysis. Blood gases were analyzed using a Ciba-Corning pH/blood gas analyzer fitted with a cooximeter. Subjects were instructed to inhale mixed gas consisting of 13% oxygen and nitrogen, which was filled in a Douglas bag, via a face mask connected to the Douglas bag with a one-way valve. Pulmonary function test was performed using an Autospirometer System 9 (Minato Medical Corporation) within one week after the right heart catheterization.

Protocol

When subjects were instructed to inhale the room air, PCWP, MPAP, MRAP, MAP and CO were determined. Then, a Swan-Ganz catheter was left in the main pulmonary artery (MPA) to collect blood samples from the PA for AM level determination and for blood gas analysis. Blood samples were also collected from the FA. Subsequently, patients were instructed to inhale a mixed gas containing 13% oxygen and nitrogen using a face mask, and MPAP and MAP were determined continuously. Fifteen minutes later, PCWP, MPAP, MRAP, MAP and CO were redetermined. Simultaneously, blood samples were again collected from the PA and FA for AM level determination and for blood gas analysis. The face mask was removed from the subjects immediately after the final collection. There were no early or late side effects observed after right heart catheterization or 13% oxygen inhalation in any patient.

Measurement of AM

Plasma AM concentrations were analyzed before and after hypoxia. Blood samples for analysis of AM were drawn by ice-chilled syringe, transferred into polypropylene tubes containing EDTA and Aprotinin and stored at 0℃. Plasma was separated by centrifugation for 15 minutes at 0℃ and immediately frozen and stored at -70℃ until radioimmunoassay (RIA). Plasma AM concentrations were determined by RIA, as previ-

ously described and compared with mean peripheral blood concentrations reported for normotensive subjects (18 ± 2 pg/ml).[12]

Statistical analysis

All data are expressed as mean ± SD. Within-group comparisons were made using paired t-tests, and between-group comparisons were made using unpaired t-tests. $P < 0.05$ was considered significant.

Results

During room air inhalation, the circulation kinetics of all subjects remained within the normal range (heart rate, HR: 77.3 ± 11.3 beats/min, PCWP: 5.2 ± 2.8 mmHg, MPAP: 14.3 ± 4.2 mmHg, MRAP: 2.4 ± 1.9 mmHg, MAP: 103.8 ± 13.9 mmHg, CI: 3.3 ± 0.8 l/min /m^2). Plasma AM levels did not differ significantly between samples taken from the PA and FA (71.9 ± 69.8 pg/ml, and 61.1 ± 46.5 pg/ml, respectively) (Fig. 1). Table 3 shows circulation kinetics, blood gases and AM levels determined 15 minutes after hypoxic loading. Arterial oxygen tension (PaO_2) and pulmonary arterial oxygen tension (PvO_2) were significantly decreased under hypoxic loading. The increased HR reflected the decreases in PaO_2 and PvO_2, PCWP, MRAP, MAP and CI did not change under hypoxic loading; however, MPAP, TPR and PVR were increased significantly. AM levels in PA and FA did not change after hypoxic loading.

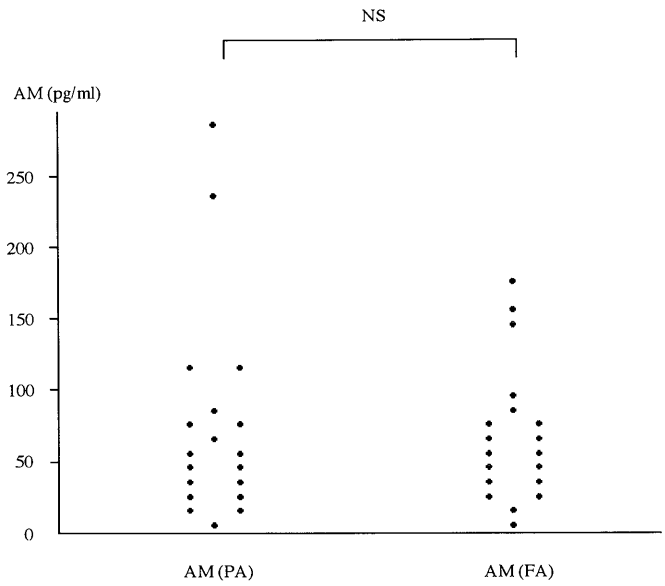

Fig. 1. Comparison of baseline plasma PA and FA AM concentrations in 19 patients with chronic respiratory disease. AM: adrenomedullin, PA: the pulmonary artery, FA: the right femoral artery, NS: not-significant.

Based on changes in MPAP before and after hypoxic loading (ΔMPAP), subjects were classified into two groups [responders (R group, ΔMPAP ≧ 5mmHg) and non-responders (NR group, ΔMPAP < 5mmHg)]. When subjects inhaled room air, TPR and PVR were higher in the R group than in the NR group. The magnitude of change in TPR (ΔTPR) was significantly greater in the R group compared with the NR group (95.5 ± 58.2 dyne·sec·cm^{-5}, and 27.5 ± 44.0 dyne·sec·cm^{-5}, respectively; $P < 0.05$). In contrast, the change in CI (ΔCI) did not

Table 3. Pre-hypoxic and hypoxic hemodynamic values and blood gas and plasma AM levels.

	Room air	13%O_2	P value
HR (beats/min)	77.3 ± 11.3	91.5 ± 12.0	< 0.01
PCWP (mmHg)	5.2 ± 2.8	5.4 ± 2.8	NS
MPAP (mmHg)	14.3 ± 4.2	19.7 ± 6.0	< 0.01
MRAP (mmHg)	2.4 ± 1.9	2.2 ± 2.1	NS
MAP (mmHg)	103.8 ± 13.9	107.7 ± 18.1	NS
CI (l/min/m^2)	3.3 ± 0.8	3.5 ± 0.5	NS
TPR (dyne·sec·cm^{-5})	249.0 ± 84.2	315.9 ± 115.3	< 0.01
PVR (dyne·sec·cm^{-5})	156.5 ± 65.2	228.9 ± 97.1	< 0.01
$PaCO_2$ (Torr)	41.1 ± 4.7	39.2 ± 3.0	< 0.01
PaO_2 (Torr)	86.5 ± 13.9	44.1 ± 6.2	< 0.01
PvO_2 (Torr)	42.3 ± 8.4	31.3 ± 2.9	< 0.01
AM (PA) (pg/ml)	71.9 ± 69.8	65.3 ± 57.5	NS
AM (FA) (pg/ml)	61.1 ± 46.5	56.2 ± 34.8	NS

Values are means±SD. HR: heart rate, PCWP: pulmonary capillary wedge pressure, MPAP: mean pulmonary arterial pressure, MRAP: mean right atrial pressure, MAP: mean arterial pressure, CI: cardiac index, TPR: total pulmonary resistance, PVR: pulmonary vascular resistance, $PaCO_2$: arterial carbon dioxide tension, PaO_2: arterial oxygen tension, PvO_2: pulmonary arterial oxygen tension, AM: adrenomedullin, PA: the pulmonary artery, FA: the right femoral artery, NS: not-significant.

Table 4. Main functional and hemodynamic values in responders and non-responders.

	Responders (n=11)	Non-responders (n=8)	P value
Age (years)	66.2 ± 7.7	62.8 ± 7.1	NS
FEV_1/FVC (%)	74.3 ± 14.3	70.6 ± 22.0	NS
VC (%predicted)	77.5 ± 27.3	83.3 ± 21.9	NS
DLCO (%predicted)	72.7 ± 25.1	72.8 ± 29.8	NS
$PaCO_2$ (Torr)	41.6 ± 5.0	40.4 ± 4.5	NS
PaO_2 (Torr)	86.7 ± 13.5	86.3 ± 15.3	NS
PvO_2 (Torr)	40.8 ± 2.5	44.3 ± 12.7	NS
MPAP (mmHg)	15.4 ± 4.8	12.9 ± 2.6	NS
CI (l/min/m^2)	3.1 ± 0.6	3.5 ± 1.1	NS
TPR (dyne·sec·cm^{-5})	281.4 ± 86.9	204.6 ± 59.7	< 0.05
PVR (dyne·sec·cm^{-5})	189.9 ± 62.1	110.6 ± 35.3	< 0.01

Values are means±SD. FEV_1/FVC: forced vital capacity expired in 1s, VC: vital capacity, DLCO: carbon monoxide diffusing capacity, $PaCO_2$: arterial carbon dioxide tension, PaO_2: arterial oxygen tension, PvO_2: pulmonary arterial oxygen tension, MPAP: mean pulmonary arterial pressure, CI: cardiac index, TPR: total pulmonary resistance, PVR: pulmonary vascular resistance, NS: not-significant.

differ significantly between these two groups (0.28 ± 0.38 l/min/m^2, and 0.15 ± 0.87 l/min/m^2, respectively). There were no significant differences in age, pulmonary function or blood gases (Table 4). There were no significant differences between these two groups in plasma AM levels from the PA and FA samples [R (PA): 61.9 ± 73.7 pg/ml, and NR (PA): 85.8 ± 66.4 pg/ml, and R (FA): 50.6 ± 42.4 pg/ml, and NR (FA): 75.5 ± 50.7 pg/ml, respectively)]. PA and FA plasma AM levels did not change significantly after hypoxic loading (Fig. 2).

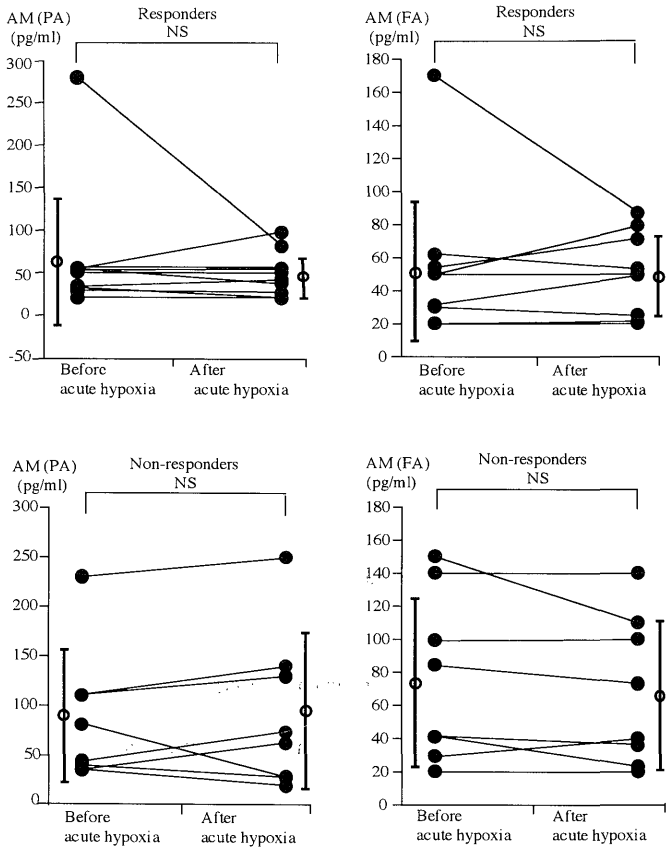

Fig. 2. Changes in AM after acute hypoxia. AM: adrenomedullin, PA: the pulmonary artery, FA: the right femoral artery, Responders: changes in mean pulmonary arterial pressure before and after hypoxic loading (ΔMPAP) ≧ 5 mmHg, Non-responders: ΔMPAP < 5 mmHg, NS: not-significant.

Discussion

Adrenomedullin (AM), consisting of 52 amino acids, has one intramolecular disulfide bond and shows slight homology with calcitonin gene-related peptide (CGRP).[5] The vasodilative action of AM is equivalent to that of CGRP, the most potent previously-known vasodilative peptide. Plasma AM levels have been reported to increase in heart failure and hypertension,[13,14] and have been positively correlated with pulmonary arterial pressure (PAP).[15] Moreover, when pulmonary hypertensive rats treated with monocrotaline were compared with healthy control rats, AM levels in the right ventricle and peripheral blood were observed to be significantly higher in the monocrotaline-treated rats than in the control rats, and high mRNA expression levels were observed in the right ventricle of the treated rats.[16] When human AM was injected into rats via the carotid artery, PAP did not change.[17] However, AM decreased PAP dose-dependently after pulmonary vascular contractility had been increased by U-46619, an analog of thromboxane A_2.[17,18] The action of AM in the pulmonary circulation was contrary to the increase in PAP.

It is generally accepted that the rise in PAP during acute hypoxia in healthy subjects is due to the combined effect of increased PVR and increased CI.[19-21] In patients with chronic respiratory disease with pulmonary hypertension, Saadjian et al.[22] showed that hypoxic breathing further increased MPAP but did not affect CI. A significant elevation in MPAP, TPR and PVR but not significant elevation in CI was observed during hypoxic breathing in ours subjects. ΔTPR was significantly higher in the R group compared with the NR group, while ΔCI was not different between these two groups. This finding suggests that the magnitude of the rise in PAP during hypoxia depends on pulmonary vascular reactivity.

It has been reported that pulmonary vascular response to acute alveolar hypoxia differs among individuals and species. The number of VSMC of the PA as well as different reactivities of substances that were released in response to acute hypoxia can be attributed to these differences in pulmonary vascular response.[25,26] In the present study, pulmonary vascular response to acute hypoxia varied, resulting in the classification of 42% of patients as non-responders. Beard *et al.* reported 28% of healthy subjects that did not respond to hypoxia [fractional concentration of oxygen in inspired gas (FiO_2) = 12%],[27] Fishman *et al.* reported 50% (FiO_2 = 12 - 14%). Furthermore, Weitzenblum *et al.* reported 50% of patients with chronic bronchitis to be non-responders to hypoxia (FiO_2 = 13%).[28]

In the present study, plasma AM levels were higher in patients with chronic respiratory disease than in normotensive subjects and there were no significant differences between PA and FA AM levels in patients with chronic respiratory disease. This differed from results reported in previous studies. Moreover, AM levels in PA and FA did not change after hypoxic loading. No significant differences in plasma AM levels were observed between the R and NR groups (Fig. 2). These

results suggest that pulmonary vascular response to acute hypoxia is not related to AM release. Moreover, AM did not appear to decrease the acute hypoxia-induced pulmonary vascular response in patients with chronic respiratory disease. When ΔMPAP was evaluated after inhalation of air containing 2% oxygen for 8 minutes in rats, ΔMPAP was significantly decreased in the rats treated with AM in comparison to that in rats without the treatment. The decrease in ΔMPAP tended to be AM dose-dependent. In rats exposed to hypoxia for 7 days, ΔMPAP was further markedly decreased. In a binding experiment using ^{125}I-AM, although the number of AM receptors in the lung showed a greater increase in chronic hypoxic rats than in control rats, levels of AM mRNA expression did not change.[29] These findings indicate that AM might be related to acute hypoxia-induced pulmonary vascular response in some way. In the present study, we determined AM levels in PA and FA blood. During acute hypoxia, if AM is released into the pulmonary tissue or the number of AM receptors increase in the lung, such changes may not be reflected by plasma AM levels. Moreover, since hypoxia was induced for only a short time (15 minutes), plasma AM levels might not have been apparent.

When healthy persons without history of cardiopulmonary disease are subjected rapidly to high-altitudes, high-altitude pulmonary edema (HAPE) sometimes occurs. HPV is reported as a major factor in HAPE. Thus, it is reported that the pulmonary vascular response to acute hypoxia is increased in HAPE patients in comparison to that in healthy subjects. Therefore, HAPE patients may have a constitutional abnormality in adaptation to high-altitudes.[30] When acute hypoxia (10% oxygen for 15 minutes) was induced in both HAPE patients and healthy subjects to determine endothelin-1 (ET-1) levels in the peripheral blood, no significant differences were observed between the two groups either before or after hypoxic loading.[31] In the cultured rat VSMC, rat or human AM was shown to inhibit ET-1 production induced by thrombin and platelet-derived growth factors. Moreover, rat or human AM increased intracellular cAMP levels, which correlated with the inhibition of ET-1 production. However, neither rat nor human AM decreased baseline ET-1 production.[32] Therefore, it is speculated that AM acts in part on ET-1 production in VSMC in a paracrine manner, thus controlling vascular response. Since AM and ET-1 act in both paracrine and autocrine manners, such changes in AM may not be reflected in plasma AM levels.

In summary, AM did not appear to be related to acute pulmonary vascular response in patients with chronic respiratory disease. However, various issues remain to be clarified. Therefore, further evaluations are necessary.

Acknowledgment

We would like to thank the doctors who contributed to this study.

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