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Pulmonary artery dysfunction in chronic thromboembolic pulmonary hypertension

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ABSTRACT

Background: Unresolved thromboemboli in the pulmonary arteries (PA) is known to cause chronic thromboembolic pulmonary hypertension (CTEPH). However, it remains unknown if vascular dysfunction in pulmonary arteries exists in patients with CTEPH.

Methods and results: We enrolled 7 female patients with CTEPH in this study, who have stable pulmonary hemodynamics after balloon pulmonary angioplasty (age; 73.6 ± 3.0 years old, mean right atrial pressure; 4.1 ± 0.4 mm Hg, mean pulmonary arterial pressure; 29.4 ± 2.7, mean pulmonary artery wedge pressure; 8.1 ± 1.2, pulmonary vascular resistance; 397.3 ± 51.7 dynes, cardiac index; 3.1 ± 0.2 L/min/m^2). Pulmonary artery vascular function was evaluated by measuring pulmonary artery vasomotion in response to acetylcholine (Ach) at 10-month follow-up after balloon pulmonary angioplasty. All pulmonary vasoactive drugs were discontinued on the day of the procedures. The endothelium-dependent vasomotor response was evaluated by intrapulmonary artery infusion of Ach at the dose of 10^{-8} mol/l, and the vaso-spastic response was at 10^{-6} mol/l. We evaluated vasomotor responses at the same segment in each patient, by measuring % changes of luminal area detected by quantitative pulmonary arterial optical frequency-domain imaging (OFDI), where OFDI catheter was fixed during the procedure. Endothelial dysfunction was observed at the dose of Ach at 10^{-8} mol/l and vasoconstriction was also confirmed at the dose of Ach at 10^{-6} mol/l in the diseased pulmonary arteries in CTEPH.

Conclusions: These results indicated that the pulmonary artery dysfunction exists in patients with CTEPH, which may be involved in the pathogenesis and progression of CTEPH.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the distinct disease entities of pulmonary hypertension (PH), characterized by obstruction of major pulmonary artery by organized thrombosis and pulmonary vascular remodeling [1,2]. CTEPH is relatively rare, but leads to increased pulmonary vascular resistance, progressive pulmonary hypertension and right heart failure to death [1,3]. CTEPH has been considered to occur following acute pulmonary embolism or recurrent pulmonary embolism [4]. Recently, we have reported that thrombin activated fibrinolysis inhibitor (TAFI), which is the plasma procarboxypeptidase produced by the liver and platelets, plays an important role in the unresolved thromboemboli in the pulmonary arteries to develop CTEPH [5].

CTEPH is usually diagnosed by mismatched perfusion defects on ventilation-perfusion lung scintigraphy and chronic thromboembolic signs on computed tomography (CT) scan and/or conventional pulmonary angiography. Further, we have reported that optical frequency-domain imaging (OFDI) and pulmonary angioscopy are also able to detect thin chronic thrombus [6–8]. These techniques can be useful, especially when there are some difficulties in CT scan and/or pulmonary angiography.

In patients with pulmonary arterial hypertension (PAH), we have previously reported that vascular dysfunction exists in pulmonary arteries [9]. However, it is unknown if vascular dysfunction exists in pulmonary arteries in CTEPH. Therefore, the present study examined to clarify this issue.

2. Materials and method

This study complies with the ethical guidelines of the 1975 Declaration of Helsinki, and the Ethical Committee of Kurume University

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approved this study. All participants gave informed consent. The authors had full access to the data and take full responsibility for its integrity.

2.1. Study population

We enrolled 7 female patients in this study who were diagnosed as CTEPH, confirmed by ventilation-perfusion RI scans and computed tomography (CT), optimal coherence tomography/OFDI and/or pulmonary angiography [6–8]. After medical therapy and balloon pulmonary angioplasty (BPA) [10], we performed this study in stabilized pulmonary hemodynamics condition.

Pulmonary arterial function was evaluated by measuring pulmonary artery vasomotion in response to acetylcholine (Ach, Sigma-Aldrich, St. Louis, MO, USA) at a 10-month follow-up after BPA. All pulmonary vasoactive drugs, including prostanoids, PDE-5 inhibitors, endothelin recepter antagonists, and oxygen were discontinued on the day of the procedures. No patient received intravenous epoprostenol or treprostinil in this study. After baseline pulmonary angiography and OFDI, the endothelium-dependent vasomotor response was evaluated by intra-pulmonary artery infusion of incremental doses of Ach at 10^{-8} mol/l for 2 min, and the pulmonary artery vasoconstriction was at 10^{-6} mol/l of Ach [11]. There was an interval of at least 3 min between each infusion [11]. Thereafter, the endothelium-independent vasomotor response was tested by an intrapulmonary bolus infusion of 200 μg isosorbide dinitrate (ISDN; Eisai, Tokyo, Japan). Angiography and OFDI (Terumo, Tokyo, Japan) were repeated 2 min after each drug infusion. We evaluated vasomotor responses at the same segment in each patient, where OFDI catheter fixed during the examination. The maximal vasomotor responses to Ach and ISDN infusions were measured by % changes of luminal area detected by quantitative pulmonary arterial OFDI, which were analysed by an independent blinded observer.

2.2. Measurement of endothelial function by flow-mediated vasodilation (FMD)

Endothelial function was assessed in the brachial artery using the FMD technique by a trained ultrasonographer in a blinded manner as previously described [12]. FMD was estimated as the percent change in the vessel diameter over the baseline value at maximal dilation during reactive hyperemia.

2.3. Statistical analysis

All results are expressed as mean ± SEM. Statistical analyses were performed using Statcel (OMS Publishing Inc., Tokorozawa, Japan). *P* values of less than 0.05 were considered to be statistically significant.

3. Results

The enrolled 7 female patients with CTEPH had stable pulmonary hemodynamics after balloon pulmonary angioplasty (age; 73.6 ± 3.0 years old, mean right atrial pressure; 4.1 ± 0.4 mm Hg, mean pulmonary arterial pressure; 29.4 ± 2.7, mean pulmonary artery wedge pressure; 8.1 ± 1.2, pulmonary vascular resistance; 397.3 ± 51.7 dynes, cardiac index; 3.1 ± 0.2 L/min/m^2) (Table 1).

The intrapulmonary administration of Ach did not affect systemic blood pressure, heart rate, and mean pulmonary arterial pressure (Fig. 1A). Changes in the vessel area in response to Ach and ISDN infusions were calculated as the percentage of change versus baseline area. Endothelial dysfunction was observed at the dose of Ach at 10^{-8} mol/l and vasoconstriction was also confirmed at the dose of Ach at 10^{-6} mol/l in the diseased pulmonary arteries in CTEPH (Fig. 1B, Supplementary video).

Table 1
Patient characteristics.

Age (years)	73.6 ± 3.0
Female	7 (100%)
Body mass index (kg/m^2)	21.4 ± 1.4
Smoking	0 (0%)
Hypertension	2 (28.6%)
Dyslipidemia	2 (28.6%)
LDL-cholesterol (mg/dl)	94.9 ± 9.7
HDL-cholesterol (mg/dl)	60.6 ± 4.2
Diabetes mellitus	0 (0%)
Hemoglobin A1c (%)	5.7 ± 0.1
eGFR (ml/min/1.73 m^2)	66.8 ± 6.5
NT-pro-BNP (pg/ml)	705.0 ± 514
Left ventricular ejection fraction (%)	72.0 ± 2.8
Uric acid (mg/dl)	4.4 ± 0.4
Hemodynamics	
Mean aortic pressure	97.0 ± 3.2
Mean right atrial pressure	4.1 ± 0.4
Mean pulmonary artery pressure	29.4 ± 2.7
Mean pulmonary artery wedge pressure	8.1 ± 1.2
Pulmonary vascular resistance	397.3 ± 51.7
Mixed venous oxygen saturation	67.4 ± 2.7
Cardiac index (liter/min/m^2)	3.1 ± 0.2
6-min walking distance (m)	367 ± 31.3
Medications	
Epoprostenol	0 (0%)
Soluble guanylate cyclase stimulator	3 (42.9%)
Oral prostanoid	2 (28.6%)
Phosphodiesterase type 5 inhibitor	4 (57.1%)
Endothelin receptor antagonist	2 (28.6%)
Warfarin	7 (100%)
Oxygen	5 (71.4%)

DL, low-density lipoprotein; HDL, high-density protein; eGFR, estimated glomerular filtration rate; NT-pro-BNP, N-terminal pro-brain natriuretic peptide.

We also compared the vascular function of the brachial arteries with that of the pulmonary arteries; however, there was no significant association (data not shown).

4. Discussion

The novel findings of the present study were as follows; (1) the abnormal vascular responses to Ach were observed in pulmonary arteries in patients with CTEPH, (2) there was no significant association between the abnormal vascular responses in pulmonary arteries and the endothelial function in brachial arteries in patients with CTEPH. Taken together, these results suggest that vascular dysfunction is substantially involved in the pathogenesis of CTEPH, independent of vascular function of systemic arteries. To the best of our knowledge, this is the first study that provides the abnormal vascular function in the pulmonary arteries of CTEPH in vivo.

We have previously indicated that Rho-kinase activity of circulating neutrophils was significantly increased in patients with PAH, but not in those with CTEPH [9]. We also indicated that endothelial-dependent relaxations to Ach and bradykinin was impaired in small pulmonary arteries (400–600 μm in diameter) and that serotonin-induced contractions of small pulmonary arteries (400–600 μm in diameter) via Rho-kinase pathway were significantly enhanced in patients with PAH [9]. In the previous studies of coronary artery diseases including our own [11], endothelium-dependent vasomotor response was evaluated by low dose of Ach (10^{-8} mol/l), and the vaso-spastic response was by high dose of Ach (10^{-6} mol/l). Based on the previous findings, we observed endothelial dysfunction at the dose of 10^{-8} mol/l of Ach and vasoconstriction at the dose of 10^{-6} mol/l in the diseased pulmonary arteries in CTEPH in the present study, which indicated the impaired endothelial-dependent relaxations to low-dose Ach and the hypercontractions to high-dose Ach in relatively large pulmonary arteries (2–4 mm in diameter). These pulmonary arterial abnormalities may not be associated with Rho-kinase pathway, but possibly some other

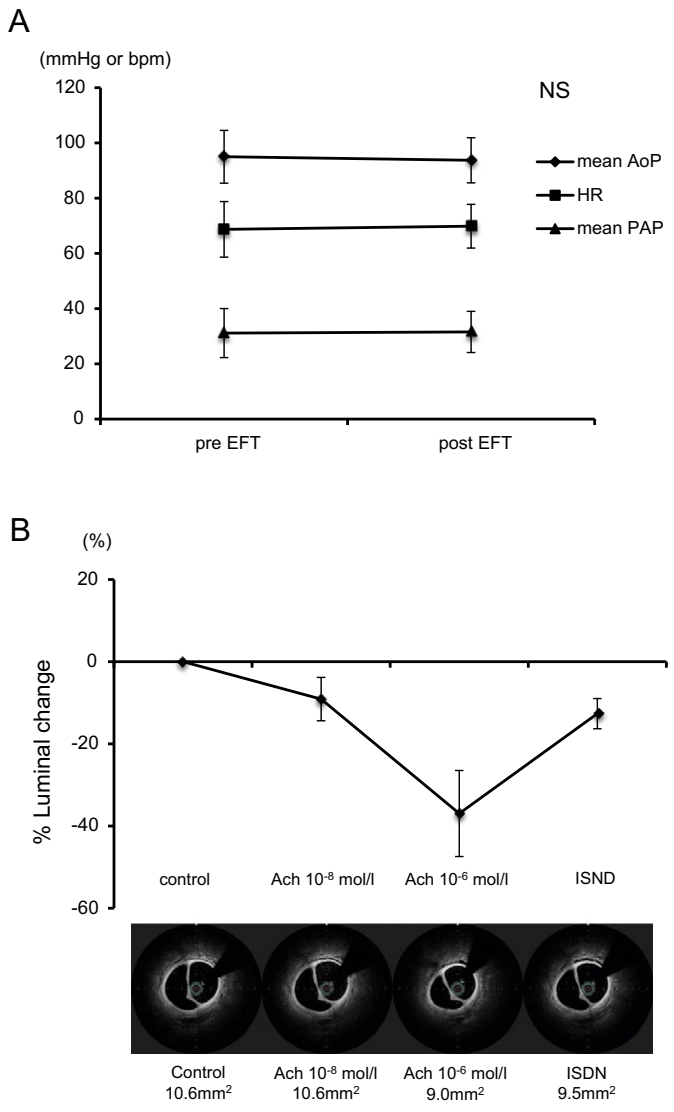

Fig. 1. A: Effects of intrapulmonary administration of acetylcholine on mean aortic pressure (AoP), heart rate (HR), and mean pulmonary arterial pressure (PAP). B: Representative optical frequency-domain imaging (OFDI) at mesh-like lesions and vasomotor responses by acetylcholine (Ach) and isosorbide dinitrate (ISDN) of the pulmonary arteries in patients with chronic thromboembolic pulmonary hypertension.

pathways, including nitric oxide-cyclic guanosine monophosphate (NO-cGMP) pathway, which may be also associated with the resistance to fibrinolysis in CTEPH [5], resulting the residual unresolved pulmonary thrombus. In such situations, TAFI, which is a plasma procarboxypeptidase produced by the liver and activated platelets, plays a key role in CTEPH [5].

There are several limitations in our study. First, we discontinued all pulmonary vasoactive drugs, including prostanoids, PDE-5 inhibitors, endothelin recepter antagonists on the day of the procedures. Due to the ethical reasons, we considered that it was the maximum "was out period"; however, it might not be long enough to observe the pulmonary artery dysfunction. Second, we simply used the similar technique to our previous study of coronary artery disease [11], to observe endothelial dysfunction and vasoconstriction in pulmonary arteries. Data in more details in this issue should be required in future studies.

Pulmonary vasodilators have been already available in CTEPH; however, the new therapeutic strategies to improve pulmonary artery dysfunction, not only hypercontraction but also endothelium-related dysfunction, should be developed in near future.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2017.09.001.

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