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Right ventricular sugars and fats in chronic thromboembolic pulmonary hypertension

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ABSTRACT

Background/objectives: Several studies have already shown the correlation between the right ventricle (RV) hemodynamic values and either glucose uptake or fatty acid uptake in the RV, respectively. However, there are few studies to compare the RV metabolic alteration before and after treatment for pulmonary hypertension. The aims of this study are to assess right ventricular glucose and fatty acid in chronic thromboembolic pulmonary hypertension (CTEPH) patients before and after pulmonary thromboendarterectomy and to examine whether there is a correlation between right ventricular glucose and fatty acid uptake.
Methods: To assess glucose and fatty acid accumulation in the RV, [^{18}F] fluoro-2-deoxyglucose (FDG)-positron emission tomography (PET) and ^{123}I-β-methyl iodophenyl pentadecanoic acid (BMIPP) imaging were performed in CTEPH patients before (FDG: n = 20, BMIPP: n = 13) and after (FDG: n = 12, BMIPP: n = 8) thromboendarterectomy.
Results: Both [^{18}F] FDG uptake and ^{123}I-BMIPP uptake in RV of post-PEA patients obviously decreased after this operation procedure ($p < 0.01$). The right ventricle [^{18}F] FDG uptake was also significantly correlated with ^{123}I-BMIPP uptake ($r = 0.45$, $p = 0.04$).
Conclusions: In this study, we observed that both glucose and fatty acid accumulated in the RV of patients with CTEPH. Although the exact details of the altered energy metabolism in the stressed RV remain unknown, this is the first study to evaluate both glucose and fatty acid uptake before and after thromboendarterectomy in patients with CTEPH, even though the number of the patient is limited.
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1. Introduction

It is generally acknowledged that there is a competition between glucose and fatty acid substrates in the heart, due to the "Randle Cycle" [1]. The Randle Cycle also known as the glucose-fatty acid cycle is a mechanism that is based on the competition between glucose and fatty acid for their uptake and oxidation in muscle and adipose tissue. There are few studies regarding this cycle in the right ventricle (RV) of patients with pulmonary hypertension (PH). In our previous study, ^{123}I-β-methyl iodophenyl pentadecanoic acid (BMIPP) imaging demonstrated that fatty acid accumulation was increased in the RV of patients with chronic thromboembolic pulmonary hypertension (CTEPH) before pulmonary thromboendarterectomy in comparison to control subjects and post-operative patients, and that its accumulation in the RV was significantly correlated with pulmonary hemodynamics [2].

RV hypertrophy in sever pulmonary arterial hypertension (PAH) is an adaptive response which requires a match between myocardial mass and a functional microcirculation in order to preserve nutrient delivery (PH) [3]. Frequently in severe PAH, the right ventricle is ischemic due to reduced coronary blood flow as a consequence of systolic compression [4], systemic hypotension [5], and right ventricular microvessel loss [6], all contributing to impaired metabolism. Moreover, epigenetic dysregulation in the right ventricle leads to impaired angiogenesis [7] and micro RNA alteration due to inflammation triggers

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changes in metabolisms in the right ventricle [8]. Recently, it has been demonstrated that, in PAH, the right ventricular myocardium undergoes a mitochondrial metabolic shift toward glycolysis which is predominant over glucose oxidation [9–12]. In RV hypertrophy increased glucose accumulation is confirmed by [^{18}F] fluoro-2-deoxyglucose (FDG)-positron emission tomography (PET) imaging both in rodent and human RV hypertrophy [9,13].

Several studies have already shown the correlation between the RV hemodynamic values and either glucose uptake or fatty acid uptake in the RV, respectively [9,14,15]. However, there are few studies to compare the RV metabolic alteration, which includes both glucose and fatty acid, before and after treatment for pulmonary hypertension. The aims of this study are to simultaneously assess right ventricular glucose and fatty acid in chronic thromboembolic pulmonary hypertension (CTEPH) patients before and after pulmonary thromboendarterectomy and to examine whether there is a correlation between right ventricular glucose and fatty acid uptake.

2. Methods

2.1. Patients

In the current study, 20 pre-operative CTEPH patients were enrolled from May 2012 to July 2015. The CTEPH diagnosis was confirmed and their operability was accessed by using right heart catheterization, pulmonary angiography, ventilation/perfusion scanning and high-quality multidetector computed tomography pulmonary angiography [16]. To exclude coronary heart disease, a computerized tomography (CT) coronary angiogram was also performed in all patients. Subsequently all 20 patients underwent thromboendarterectomy which was performed by Dr. Keiichi Ishida at the Chiba University Hospital, Japan. To assess post-operative hemodynamics right heart catheterization and pulmonary angiography were performed again approximately 1 year after thromboendarterectomy in 12 patients. Of the 20 patients who underwent pulmonary thromboendarterectomy, [^{18}F] FDG-PET imaging was performed in all patients at 2 weeks before thromboendarterectomy, and in 12 at 1 year after thromboendarterectomy. Of these 20 patients, ^{123}I-BMIPP study was also done in 13 patients at 2 weeks before thromboendarterectomy, and in 8 at 1 year after thromboendarterectomy. Thirteen patients had an evaluation of both imaging modalities before thromboendarterectomy and 7 patients did at before and after thromboendarterectomy. Of the 13 patients who were examined using ^{123}I-BMIPP imaging, 11 patients were included in our previous report [2]. A signed informed consent document was obtained from all patients who underwent this analog imaging. This study was approved by the Research Ethics Committee of Chiba University School of Medicine.

2.2. Imaging protocols

2.2.1. FDG-PET imaging

Twenty patients at 2 weeks before thromboendarterectomy and 12 at 1 year after thromboendarterectomy underwent [^{18}F] fluorodeoxyglucose (FDG) positron-emission tomography (PET) (Biograph mCT Flow 20-4R; SIEMEN, Berlin, German). Sixty minutes after the intravenous injection of 185 MBq of [^{18}F] FDG, PET image acquisition was performed. Each patient fasted at least 12 h before this study. The patients received [^{18}F] FDG intravenously 60 min after oral 75 g glucose loading. Blood glucose, free fatty acid and insulin levels were measured just before [^{18}F] FDG administration. All PET imaging data were evaluated by an experienced investigator who was blinded to the clinical histories of the patients. By using [^{18}F] FDG-PET imaging, glucose accumulation in the right ventricle was quantified. The images with transaxial slices at 4 mm intervals to cover the whole cardiac region were provided from the scanner. A maximum body weight-corrected standardized uptake value (SUV) of [^{18}F] FDG accumulation in the right ventricular myocardium was obtained from the calculated pixel activity. This imaging underwent 2 days before BMIPP fatty acid imaging.

2.2.2. BMIPP fatty acid cardiac scintigraphy

Detailed protocols for this imaging modality have been described in our previous publication briefly [2]. ^{123}I-BMIPP study was done in 13 patients at 2 weeks before thromboendarterectomy, and in 8 at 1 year after thromboendarterectomy (Infinia Hawkeye 4, GE Healthcare Japan Co. Ltd.). Planar image acquisition was done for 5 min with the extended low-energy general-purpose parallel-hole collimator's 64 × 64 matrix, 40 min after intravenous administration of ^{123}I-BMIPP. To optimize image to separate the right ventricle from the left ventricle, the planar image was performed in the left anterior oblique position. The energy window of ^{123}I was centered at 159 keV ± 10%.

2.2.3. A 320-slice computed tomography (CT)

By using electrocardiogram-gated enhanced volume scanning using 320-slice CT (Aquilion One, Toshiba Medical, Tochigi, Japan) with a 0.5 mm slice thickness and 0.35 s/rotation, right ventricular wall thickness was evaluated in 10 patients who underwent [^{18}F] FDG-PET imaging at pre- and post-thromboendarterectomy. Detailed protocols for this CT have been described in our previous publication [2].

2.3. Statistical analysis

Data analysis was performed using the JMP© 9.0.0 (Japanese version, SAS Institute Inc., Tokyo, Japan). All numeric values are expressed as mean ± standard deviation (SD). The baseline data and the hemodynamic values were compared using paired Student's t-tests. Spearman's rank correlation coefficient was utilized to compare the two variables. A p value of 0.05 was considered to be statistically significant.

3. Results

3.1. Clinical characteristics

Twenty CTEPH patients who underwent thromboendarterectomy were enrolled in the current study. The mean age of the patients was 60.3 ± 10.6 years (range: 38 to 73) and the male to female ratio was 1:4, respectively (Table 1).

The surgery improved the New York Heart Association (NYHA) functional class, the 6-minute walk test, and the hemodynamic parameters obtained by right heart catheterization, including mean pulmonary artery pressure, pulmonary vascular resistance, mixed venous oxygen pressure, and alveolar-arterial oxygen pressure difference. Between groups before and after pulmonary thromboendarterectomy, there were statistically significant differences in the 6-minute walk test (376.54.6 ± 100.6 m vs. 467.9 ± 145.7 m, respectively; $p < 0.05$), mean pulmonary artery pressure (42.9 ± 10.7 mm Hg vs. 23.3 ± 7.2 mm Hg, respectively; $p < 0.01$) (Fig. 1a), pulmonary vascular resistance (Wood units) (8.3 ± 3.7 vs. 3.7 ± 1.9, respectively; $p < 0.01$) (Fig. 1b), mixed venous oxygen pressure (PvO_2) (34.0 ± 3.4 mm Hg vs. 40.0 ± 4.1 mm Hg, respectively; $p < 0.01$), alveolar-arterial oxygen pressure difference ($A\text{-}aDO_2$) (46.6 ± 9.0 mm Hg vs. 21.9 ± 15.0 mm Hg, respectively; $p < 0.01$) (Table 1). However, there was no significant difference in the cardiac index (3.0 ± 0.8/min/m^2 vs. 2.8 ± 0.8 l/min/m^2, respectively; $p = 0.0.22$) (Fig. 1c).

In 6 of 10 patients who were treated with vasodilator drugs before thromboendarterectomy, these drugs became unnecessary post-surgery. Of 11 patients, this surgery resulted in weaning 4 patients off from home oxygen therapy (HOT) (Table 1).

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