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Evaluation of right ventricular myocardial metabolism and pulmonary vascular remodeling in pulmonary arterial hypertension by positron emission tomography

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Abstract

Pulmonary arterial hypertension (PAH) is a rare and severe form of pulmonary hypertension, which is characterized by pulmonary vascular remodeling, as well as metabolic and functional alterations in the right ventricular myocardium. The proven metabolic shift towards anaerobic glycolysis in the heart and lungs can be quantitatively and qualitatively evaluated with a molecular imaging technique — 2-[18F] fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET). This review is devoted to the analysis of foreign scientific publications. There are presented research results that prove the diagnostic value of fused PET/computer tomography (CT) (PET/CT) images with FDG and other promising radiopharmaceuticals in patients with PAH. This tool allows estimation of the severity of the disease, to determine the clinical prognosis and monitor the effectiveness of treatment in each case. Furthermore, the methods of molecular visualization allow the analysis of the PAH pathogenesis and description of the new biologic targets, such as development factors of endothelial dysfunction and remodeling of pulmonary vasculature.

Key words: positron emission tomography, pulmonary hypertension, pulmonary vascular remodeling, 2-[18F] fluoro-2-deoxy-D-glucose, computer tomography, right ventricular metabolism

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Позитронная эмиссионная томография в оценке метаболизма миокарда правого желудочка и ремоделирования сосудов малого круга кровообращения при легочной артериальной гипертензии

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Резюме

Легочная артериальная гипертензия (ЛАГ) является редкой и клинически неблагоприятной формой легочной гипертензии, для которой характерны ремоделирование сосудов малого круга кровообращения, а также обменные и функциональные нарушения в миокарде правого желудочка. Доказанная смена путей метаболизма на анаэробный гликолиз в сердце и легких может быть количественно и качественно оценена с помощью метода молекулярной визуализации — позитронной эмиссионной томографии (ПЭТ) с ^{18}F-фтордезоксиглюкозой (^{18}F-ФДГ). В настоящей статье проведен анализ зарубежной литературы, представлены результаты исследований, подтверждающих диагностическую значимость выполнения процедуры ПЭТ, совмещенной с компьютерной томографией (КТ), с ^{18}F-ФДГ и другими перспективными радиофармацевтическими препаратами у пациентов с ЛАГ. Данная методика позволяет оценить тяжесть заболевания, определить клинический прогноз и сделать вывод об эффективности проводимого лечения в каждом конкретном случае. Кроме того, методы молекулярной визуализации предоставляют возможность проанализировать патогенетическую основу ЛАГ и рассмотреть новые биологические мишени, такие как факторы развития эндотелиальной дисфункции и ремоделирования сосудов малого круга кровообращения.

Ключевые слова: позитронная эмиссионная томография, легочная гипертензия, ремоделирование легочных сосудов, компьютерная томография, фтордезоксиглюкоза, ^{18}F-фтордезоксиглюкоза, метаболизм правого желудочка

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Pulmonary arterial hypertension (PAH) is a rare form of pulmonary hypertension (PH), which is based on primary damage of the lung microvasculature and gradual obliteration of the lumen in distal pulmonary arteries and arterioles [1]. The pulmonary vascular pathology in PAH is characterized by structural remodeling of small arteries and arterioles with proliferation of endothelial and smooth muscle cells, that results in vessel medial wall thickening due to deposition of collagen and macrophage infiltration. The elevation of pulmonary vascular resistance leads to right ventricle overload with subsequent development of right heart failure — the leading cause of death for patients with PAH.

The morphologic changes of right ventricle in PAH include myocardial hypertrophy, increased systolic pressure and end-diastolic volume with progressive ventricular dilatation, which are associated with decreased right coronary artery perfusion and alteration of cardiac energy metabolism with an increased glycose utilization [2, 3]. As a result of developing ischaemia the myocardium shifts from more efficient oxidative phosphorylation to anaerobic glycolysis. This metabolic impairment leads to right ventricle dysfunction, reduced RV contractility and decreased cardiac output [4, 5]. It is worth noting, there is an alternative point, according to which the pathologic metabolic shift in patients with PAH can occur in the absence of ischemia [6, 7].

The described metabolic shift to the glycolytic pathway with a lower energy yield and overexpression of the glucose transporter GLUT1 result in compensatory increased glucose uptake by altered cells, that can be quantitatively evaluated with a molecular imaging technique — 2-[18F] fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET).

In the study with experimental animal models Izquierdo-Garcia J.L. et al. [8] reported significantly higher ^{18}F-FDG uptake in the lung parenchyma and both ventricles in the PAH than in the control group. The PET procedure was performed with experimental mice after fasted period overnight. For evaluation of radiopharmaceutical uptake in the both ventricles and lungs, three-dimensional regions of interest were drawn for each of them and the maximum standardized uptake value (SUVmax) was quantified [8]. The metabolic remodeling in the PAH heart and lungs was previously described in several PET studies with experimental animal models [9] and patients with PAH [5, 10]. Preliminary data demonstrated the correlation between high ^{18}F-FDG uptake in the right ventricle and severity of the disease [11]. Saygin et al. [12] performed the study quantitatively investigating metabolic and functional changes in the right ventricle by gated ^{18}F-FDG PET/CT scanning, they also evaluated metabolic remodeling in the lung parenchyma of patients with PH in comparison to healthy controls. In this study the most individuals with PH had proven heritable or idiopathic forms of PAH. According to the scan protocol, PET metabolic images were acquired after the fasting state for 8 h and the regions of interest were located in the heart and the most part of the lung. Using the specific tool of an image processing workstation allowed the calculation of the right ventricle ejection fraction. The researchers drawn the regions of interest on static cardiac PET/CT images to count SUVmax in the left ventricular and right ventricular free walls with calculation of their ratio $SUVmax_{RV}/SUVmax_{LV}$, in the right atrial free wall and in the interventricular septum. In order to assess lung FDG uptake, the mean standardized uptake value (SUVmean) was calculated as the average over the 24 regions in the lung parenchyma. The obtained lung and myocardial SUV measurements capturing the glucose metabolism, along with PET cardiac functional measurements in the right ventricle were all significantly higher in individuals with PH compared to healthy controls [12]. Even more, PET right ventricular volumes and the relative indicator of myocardial glucose metabolism $SUVmax_{RV}/SUVmax_{LV}$ closely correlated with plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and a number of ECHO parameters including: right ventricular end-diastolic and end-systolic areas, TAPSE (tricuspid annular plane systolic excursion), right ventricular systolic pressure (RVSP), Tei index (myocardial performance index) and right ventricular global peak systolic strain.

In a study of Kluge et al. [13] the authors investigated the relationship between right-to-left ratios of glucose uptake SUV_{RV}/SUV_{LV} and severity of PH (the patients with PH associated with left heart disease (group 2) were excluded). They found that right ventricular metabolic rate of glucose uptake

positively correlated with NYHA functional class and Tei-index. It should be noted, in this study patient preparation included administration of an oral glucose load in order to inhibit fatty acids oxidation in the right ventricle. It was mentioned, that the increased ratio of glucose metabolism SUV_{RV}/SUV_{LV} was based on decreasing left ventricular glucose uptake as a result of reduced work load [13].

On the other hand, Hagen et al. [10] reported that the ratio SUV_{RV}/SUV_{LV} elevated due to absolute increase in right ventricular glucose uptake. In the other study Can et al. [14] showed the same results: SUV_{RV}/SUV_{LV} was significantly higher in patients with PAH than in the control group, correlating with ECHO parameters and 6-min walking distance. Bokhari et al. [15] also demonstrated the relation between SUV_{RV}, SUV_{RV}/SUV_{LV} and pulmonary artery pressure recorded in right heart catheterization (RHC). In the study of Ohira et al. [16], the authors reported that the ratio SUV_{RV}/SUV_{LV} strongly correlated with the degree of pressure increase in PAH as follows: the patients with mean pulmonary artery pressure (mPAP) < 35 mmHg had $SUV_{RV}/SUV_{LV} < 1$ and the patients with a mPAP ≥ 50 mmHg had $SUV_{RV}/SUV_{LV} > 1$. The researchers concluded that was mainly due to the elevation of right ventricular pressure overload in patients with PAH [16].

The interesting results were obtained by Oguz et al. [17], who aimed to assess the diagnostic value of ^{18}F-FDG PET/CT in the management of patients with chronic thromboembolic pulmonary hypertension (CTEPH). The authors reported the negative correlation between 6-min walking distance and SUV_{RV}/SUV_{LV} ratio. Consequently, ^{18}F-FDG PET/CT can be an alternative to classic clinical tools in cases when 6-min walking test cannot be performed due to reduced exercise capacity, advanced age, orthopedic barriers and severe concomitant diseases. Furthermore the ratio SUV_{RV}/SUV_{LV} was found to be closely associated with angiographic clot burden score (Qanadli score), which determines the thrombus burden in the pulmonary arterial bed. In this way, the authors suggested that ^{18}F-FDG PET/CT is a valuable diagnostic modality for indirectly showing thrombus burden in the pulmonary vasculature and predicting thrombus amount that can be successfully removed by pulmonary endarterectomy (PEA) [17].

There is a number of scientific publications on assessment metabolic changes in the right ventricle after PAH-specific treatment by FDG PET/CT. In a study of Oikawa et al. [11], there was registered a decrease of right ventricular glucose uptake in the patients after three months therapy with epoprostenol — prostacycline analogue, which is the medication for treatment of PAH. According to Fang et al. [18], the authors reported a significant reduction in SUV_{RV}/SUV_{LV} ratio after six month treatment with sildenafil (PDE_5 inhibitor).

Since the prognosis of PAH mainly depends on right ventricular function and development of heart failure, there are several studies aiming to assess the prognostic value of ^{18}FDG PET/CT in patients with PAH. Tatebe et al. [19] described the rate of FDG uptake in the right ventricle as a significant prognostic factor, that can determine severity of the disease and effectiveness of the treatment. In a recent study of Li et al. [20], the enhanced SUV_{RV} and high SUV_{RV}/SUV_{LV} ratio were estimated as independent predictors for poor prognosis.

The reasons of metabolic impairment in the right ventricular myocardium include ischemic conditions in the cardiomyocytes due to decreased right coronary artery perfusion pressure [21]. Insufficient oxygen delivery to the myocardium leads to significant increase in anaerobic glycolysis providing a source of ATP and to the reduction in fatty-acids oxidative phosphorylation. However, this metabolic pathway of ATP production is less efficient than oxidative phosphorylation and could not support the state of compensation for a long time in severe right ventricular hypertrophy, that results in hibernation of cardiomyocytes. This statement was approved by Ohira et al. [16] in their two-step study: firstly, patients underwent PET/CT with ^{82}Rb or ^{13}N-ammonia for myocardial perfusion imaging, secondly, they undergo FDG PET/CT for myocardial metabolic imaging after the fasting period. The authors reported the perfusion/metabolism mismatch in the right ventricular myocardium in all patients with severe PAH, that supported there was a state of cardiomyocytes' hibernation [16].

Besides ^{18}F-FDG the other radiopharmaceuticals $^{15}O_2$ and $C^{15}O$ were discussed as biomarkers for oxidative metabolism in order to more detailed and rigorous investigation of metabolic alterations in the right ventricular myocardium [22]. In a study of Wong et al. the obtained data demonstrated in-

efficient myocardial oxygen utilization despite its increased uptake by right ventricular cardiomyocytes in NYHA III class patients with PAH. These results confirm the hypothesis about mitochondrial dysfunction in PAH pathogenesis. In addition, the promising radiopharmaceuticals are alpha-beta3 integrin antagonists (^{18}F-RDG) for investigation of angiogenesis [23] and ^{11}C-hydroxyephedrine for assessment of sympathetic innervation abnormalities in the right ventricle [24].

The contradictory data was obtained in two studies investigating alterations of fatty acid metabolism in the right ventricular myocardium under PAH condition using PET with ^{18}F-fluoro-6-thia-hepadecanoic acid (FTHA). In a study of Graham et al. [7], the authors demonstrated the decreased right ventricular ^{18}F-FTHA uptake in the classic experimental animal model of PAH. They considered that this reduction was due to decreased fatty acid enzymes and transporters in the cardiomyocytes, in particular lipoprotein lipase. As a result of inhibition of lipid metabolism enzymes there was the metabolic shift from fatty acids to carbohydrate energy sources. According to ^{18}F-FDG PET/CT imaging analysis, the authors reported the elevated rate of glucose uptake and enhanced anaerobic glycolysis in the right ventricular myocardium. The alternative results were obtained in the study of Ohira et al. [16], that estimated the positive correlation between FDG uptake in the right ventricle and severity of the PAH and the relation between ^{18}F-FTHA uptake in cardiomyocytes and degree of right ventricle dysfunction in patients with PAH. The authors concluded that there was increased cardiac fatty acid utilization with decline in right ventricular ejection fraction [16]. The relation between elevated ^{18}F-FTHA uptake and right ventricle dysfunction might evidence that fatty acid oxidation may contribute to the development of maladaptive right ventricular hypertrophy. Nevertheless, the authors suggested that with increase of mean pulmonary artery pressures there was the disproportionate increase of FDG uptake compared to FTHA uptake, that may represent a shift towards anaerobic glycolysis.

The mitochondrial dysfunction of pulmonary endothelial and smooth muscle cells seems to play an important role in the PAH pathogenesis [25,26]. As well as in the cardiomyocytes there is a shift in cell metabolism from oxidative phosphorylation to anaerobic glycolysis, known as Warburg effect [27]. The metabolic impairment in pulmonary vessels is presumably associated with HIF-1α factor activation, which is induced by hypoxia [28]. Kim et al. [29] showed also the upregulation of pyruvate dehydrogenase activity, which blocks the entrance of pyruvate into the Krebs cycle for subsequent oxidation.

Using PET/CT imaging Frille et al. [30] reported the increased pulmonary ^{18}F-FDG uptake in the patients with PAH (idiopathic, familial, due to connective tissue disease, congenital heart disease, etc) and with PH due to pulmonary disease and CTEPH. However, there was no significant difference in FDG uptake between patients with PH due to left heart diseases and healthy control group [31].

In the study of Frille et al. [30] the authors also investigated ^{18}F-FDG uptake in the heart and lungs of patients with different PH etiologies. Patients with an mPAP ≥ 25 mm Hg showed a significantly higher SUV in lung parenchyma, pulmonary arteries and right ventricle than patients with an mPAP < 25 mm Hg. The similar results were found for patients with a pulmonary vascular resistance (PVR) ≥ 480 dyn·s/cm^5 and < 480 dyn·s/cm^5 The FDG uptake in lung parenchyma, pulmonary arteries and right ventricle strongly correlated with RHC parameters (mPAP, PVR) and serum NT-proBNP levels. According to the results of the study, the authors concluded that pulmonary hypertension represents an angioproliferative disease regardless of etiology: primary condition as PAH or secondary due end-stage lung disease, CTEPH. The researchers also considered that proliferation of endothelial and smooth muscle cells with thickening of intima and media of pulmonary arteries might occur in the context of pulmonary vascular remodeling in patients with chronic obstructive pulmonary disease and interstitial lung diseases [32, 33]. Besides, Frille et al. concluded the metabolic changes in lung parenchyma, pulmonary arteries and right ventricle can be estimated with FDG PET/CT and depend on the severity of PH regardless of etiologic group [30].

Another biologic target for molecular visualization in PAH should be endothelial dysfunction as an early and key event in the development of pulmonary vascular pathology [34]. Several PET radiopharmaceuticals were proposed to investigate

the functions of pulmonary vascular endothelial cells, they are endothelin ET_B receptors antagonists ^{18}F-BQ-3020 [35] and inhibitors of angiotensin-converting enzyme ^{18}F-fluorocaptopril and ^{18}F-fluorolisinopril [36]. An important scientific direction is the development of labeled ligands for potential therapeutic targets such as enzyme phosphodiesterase type 5 (PDE_5). In a study of Jakobsen et al. [37], the authors showed the specific binding of radioligand ^{11}C-RAL-01PDE to PDE_5 in the heart and lungs, that quantitatively evaluated the expression of this enzyme and allowed to assess the effectiveness of using its inhibitors for therapeutic purposes.

The proliferation of endothelial and smooth muscle cells is a link of PAH pathogenesis and can be investigated by ^{18}F-FDG PET/CT. However, this tool has limitations in assessment of pulmonary vascular state because the reduced lung perfusion prevents the delivery of radiopharmaceutical to distal pulmonary arteries. Moreover ^{18}F-FDG does not bind specifically to lung vessels and may accumulate in damaged pulmonary tissue of another etiology, for instance in inflammatory foci due to diffuse parenchymal lung disease [38].

The promising results were presented in the study aiming to evaluate vascular remodeling in PAH using labeled radioligand 3′-deoxy-3′-[18F]-fluorothymidine (^{18}F-FLT) — the biomarker for cell proliferation [39]. It was previously proven that ^{18}F-FLT uptake strongly correlated with histological markers, such as proliferating cell nuclear antigen Ki-67 [40]. Ashek et al. demonstrated the high accumulation of ^{18}F-FLT in the lungs of patients with idiopathic PAH in comparison with control group using dynamic ^{18}F-FLT PET/CT. They showed the heterogeneity in the lung ^{18}F-FLT uptake between patients with IPAH, as well as within the lungs of each patient, which coincided with histopathologic reports of lungs from patients with IPAH: according to immunohistochemical analysis there was enhanced expression of thymidine kinase 1 in the remodeled vessels of IPAH patients lungs. Also the authors demonstrated by real-time polymerase chain reaction analysis that pulmonary vascular fibroblasts isolated from patients with IPAH exhibited overexpression of the thymidine kinase 1 and thymidine phosphorylase genes and the thymidine transporter ENT1.

The same results were obtained by Ashek et al. for experimental animal models of PAH. They observed increased FLT uptake in the rat lungs correlating with the Ki-67 score and subsequent decrease of FLT uptake in the remodeled vessels after antiproliferative targeted treatments. The authors confirmed the high diagnostic value of ^{18}F-FLT PET/CT for noninvasive assessment of endothelial and smoot muscle cells hyperproliferation in the pulmonary vasculature under PAH condition. Furthermore, the researchers considered that ^{18}F-FLT PET/CT may be a useful tool to evaluate novel therapies targeting the structural alterations in lung vessels and in prospect to personally select the antiproliferative targeted drugs. In comparison with ^{18}F-FDG the significant superiority of ^{18}F-FLT is the low noise in the signal and the possibility to exactly differentiate cell proliferation from inflammatory reaction [41].

Conclusion

Based on the analysis of the literature it should be recognized that the issue of studying right ventricular myocardial metabolism and proliferation of pulmonary endothelial and smooth muscle cells by PET/CT with different radiopharmaceuticals in patients with PAH is still of current interest. Positron emission tomography allows to stratify patients according to the severity of the disease and more accurately determine their prognosis. Further development of novel radionuclide techniques is needed not only for evaluation of alterations in pulmonary vessels, but also for investigation of right ventricle function, as right heart failure is exactly the leading cause of death for patients with pulmonary hypertension. In general, the use of molecular imaging techniques reveals new opportunities in the study of various biologic processes in normal and pathology, including such clinically complicated group of patients as with PAH. There is a need of future scientific researches, which aim to dynamic monitoring the status of patients with pulmonary arterial hypertension and monitoring the effectiveness of new targeted treatments.

Conflict of interest

The authors declare no conflict of interest.

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