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What is the meaning of late gadolinium enhancement in right ventricle insertion points in pulmonary arterial hypertension?

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Introduction

Cardiac magnetic resonance (CMR) allows for noninvasive assessment of myocardial edema, fibrosis or infiltration [1,2]. Presence of late gadolinium enhancement (LGE) in

myocardial walls has been found in majority of patients with cardiac diseases and is often identified as fibrotic area due to chronic overpressure and / or overload of heart [3-6]. Comparing to typical LGE localization in ventricles' free walls after ischemic events, LGE in pulmonary arterial hypertension (PAH) and hypertrophic cardiomyopathy (HCM) is mostly described in junctions of the interventricular septum and right ventricle (RV) free walls called RV insertion points (RVIPs) [7,8].

Inflammatory processes occurring in pulmonary vessels play an important role in PAH pathophysiology [9-10]. We previously confirmed that in case of RV failure and hemodynamic impairment due to PAH, changes of circulating cytokines' levels like interleukin 6 or SDF alpha are related with myocardial wall glucose metabolism alterations observed in hybrid positron emission tomography / magnetic resonance imaging (PET / MRI) [11].

We also introduced a new parameter called LGE mass index (quantitative assessment of LGE mass in RVIPs divided by body surface area) which was strongly related with RV dysfunction and predicted PAH patients' prognosis [4]. This was the opposite of the sole qualitative assessment (presence of LGE in RVIPs) assessed a few years earlier in a group of PAH patients by Swift et al [12]. As cardiac qualitative and / or quantitative assessments of LGE may vary due to natural PAH progression or specific therapy, we hypothesized that if presence of LGE at RVIPs is equivocal to abundance of fibrotic tissue (tissue with low metabolic activity), this should affect local glucose uptake in RVIPs. To juxtapose myocardial fibrosis and glucose metabolism in RVIPs and to avoid time shift in the scans we used simultaneous hybrid imaging – CMR and 18F-fluorodeoxyglucose (FDG) PET.

The main aim of the study was to a.) to evaluate the glucose metabolism in the RVIPs where LGE is qualitatively described in CMR imaging b.) assess whether local cardiac tissue changes occurring in RVIPs described as LGE pattern may alter in the course of the disease

progression and initiation of advanced targeted PAH treatment.

Patients and methods

Population characteristics

Initially twenty-eight clinically stable PAH patients (51.4 (15.9) years) had simultaneous PET / MRI scans during baseline visit. Follow up (FU) visits were done in twenty patients (4 deaths, 4 patients did not agree to participate in the FU visits) after 24 months since enrolment. Stable PAH patient was defined as a patient without any exacerbation of the main disease (not requiring hospitalization) at the moment of enrollment. The diagnosis of precapillary PAH was confirmed by right heart catheterization (RHC) according to European guidelines [13]. The exclusion criteria were the following: patients in World Health Organization (WHO) functional assessment class IV, Eisenmenger physiology, PAH associated with prevalent systemic-to-pulmonary shunts due to moderate to large defects (according to European guidelines), group II, III, IV, V of PH and contraindications to CMR. RHC was carried out during enrolment with a standard technique within median 4 [2–6] days of MRI scans using a balloon-tipped 7F Swan-Ganz catheter; cardiac output was measured by thermodilution method. The clinical follow-up lasted 24 months. Death, WHO class worsening, hospitalization due to PAH progression or right heart failure were used as composite clinical endpoint (CEP) and assessed at FU visits.

CMR imaging

CMR studies were assessed and analysed using a dedicated workstation and software as previously described [4, 14].

PET imaging

Heart glucose metabolism was assessed with FDG as a tracer in myocardial PET analysis and its uptake was quantified as mean standardized uptake value (SUV) for area of LGE in RVIPs

(SUV_{RVIPS}) [14]. PET / MRI results were not known to treating physician and did not affect the decision about the therapy, simultaneously physician analyzing the scans was not aware of the patients' clinical state.

Statistical analysis

Shapiro – Wilk test was performed for the assessment of the continuous variables' distribution. The data are expressed as a mean (standard deviation (SD)) or median [interquartile range] as appropriate; categorical values were presented by number (%). The dependent samples t-test or Wilcoxon signed rank test was used to compare matched (baseline vs follow-up) values depending on the distribution. Spearman's correlation coefficient was used to examine the relationship between two continuous variables. Benjamini–Hochberg correction was used to account for multiple comparisons in correlation analysis. $P < 0.05$ was deemed statistically significant. A statistical software package STATA13 (Stata Corporation, College Station, Texas, USA) was used for the analysis.

The study was approved by the local Bioethics Committee of the Medical University of Bialystok, Poland (R-I-002/140/2017) and all enrolled study patients provided written informed consent to participate in the study,

Results

The general characteristics of baseline and follow up groups (n = 20) including hemodynamic parameters from RHC and CMR results are presented in Table 1 (which was also published in different form in previous manuscript [4]). PAH patients were mostly (60%, n = 12) at intermediate risk of 1-year mortality according to the previous 2015 European Society of Cardiology guidelines [15]. Idiopathic/heritable PAH accounted for 60% (n = 12) of the group. Baseline mean pulmonary artery pressure (mPAP) was 50.5 (18.3) mmHg and right ventricle ejection fraction (RVEF) was 45.1 (9.6) %. LGE in RVIPs was present in all PAH

cases. LGE did not involve interventricular septum in any patients. Median baseline LGE mass in RVIPs was 5.4 [2.3–9.4] g and median SUV_{RVIPS} was 6.33 [2.5–9.9].

After 24 months from baseline visits, we performed FU visits. Twenty PAH patients remained in the study group thus we compared FU parameters' values to the corresponding baseline group (20 matched pairs). At FU, we observed significant improvement of MRI-derived RVEF (45.1 (9.6) % to 52.4 (12.9), $P = 0.01$), and in hemodynamic parameters obtained from RHC e.g., mPAP (50.5 (18.3) mmHg to 42.8 (18.6), $P = 0.03$) and PVR (8.9 (5.7) WU to 7.3 (4.7), $P = 0.04$), Table 1.

Between baseline and FU visits 16 patients (80%) had experienced clinical end-point (4 deaths, 12 had clinical symptoms of PAH progression). There was a clinical trend towards decrease of SUV_{RVIPS} in FU PET scans (5.18 [3.3–7.7] vs baseline 6.33 [2.5–9.9], mean change - 1.48, $P = 0.16$). Follow up scans also revealed clinical tendency of median LGE mass to increase (6.3 [3.4–11.4] g vs baseline 5.4 [2.3-9.4], mean change - 1.26, $P = 0.27$). No significant correlation was found between LGE mass and SUV_{RVIPS} in neither baseline nor FU scans ($R = -0.05$, $P = 0.76$ and $R = -0.08$, $P = 0.72$, respectively). There were no association between change in LGE between baseline and follow-up and change in SUV_{RVIPS} during follow-up. These data suggest that the extent of LGE is not associated with lower metabolism in RV insertion points, hence undermining fibrosis hypothesis of LGE in RVIP in PAH patients.

Discussion

Quantitative analysis of myocardial fibrosis and active inflammation (and their relationship) with a use of hybrid imaging has never been investigated in pulmonary hypertension before. We have previously confirmed that early determination of RV dysfunction, especially before clinical worsening, is possible non-invasively with the use of PET / MRI imaging [16]. This

hybrid also allows assessment of glucose metabolism of RV free wall, what was related with PAH patients' prognosis [14]. In this study, we found that PET / MRI, may be a helpful tool to evaluate previous assumptions about the cardiac LGE in PAH, what changes the perspective of routine assessment of LGE presence.

The prevalence of RVIPs LGE in severely ill PAH patients seems to be nearly universal finding (irrespective of PAH etiology) and was often considered to be a replacement fibrosis [17]. Importantly, it may also be found in apparently healthy individuals [4]. Inflammation is also a major regulator of the reparative response in tissue damage, but prolonged and uncontrolled remodeling of extracellular matrix often leads to deterioration of cardiac function and poor prognosis [18]. Now, we confirmed that local cardiac tissue changes in PAH visualized as LGE in CMR may be indeed still metabolically active and susceptible to alter under the influence of the applied PAH therapy or disease progression.

We hypothesized, that what is considered as LGE may in fact be associated with local inflammation. This underlines the importance of research into the role of inflammation in PAH pathogenesis, which may result in development of new immunomodulatory therapies targeting not only affected pulmonary vessels but also cardiac muscle.

Inflammation may become no longer active when myocardium shows advanced fibrosis and severely dyskinetic-thinned wall. Thus, areas with fibrotic tissue have poor metabolism (with decreased or minimal FDG uptake) in PET analysis, however some discrepancies were also observed [18]. Mismatch between visual assessment of fibrotic tissue in the form of CMR LGE and sustained or even increased metabolism is probably due to dominance of diffuse (interstitial) fibrosis type over typical replacement fibrosis, seen in damaged tissue. Thus CMR-derived LGE presence may be limited for the assessment of the diffuse interstitial fibrosis, which is often found in patients with hypertrophic or dilated cardiomyopathy.

There is still little evidence confirming which type of fibrosis may be found in PAH patients'

RVIPs. In our study population, almost 90% of patients had LGE pattern in insertion points. In other studies, on bigger populations and with greater spectrum of disease severity, RVIPs LGE was not so often found in mild or early-stage PAH [7]. It seems that local tissue alterations occurring in RVIPs are strongly related with progression of the disease. Thus, the exact cause of LGE in RVIPs in patients with "early stage" PAH or without RV dysfunction is still not elucidated [19].

In this study we observed variability of LGE mass in insertion points of particular PAH patients. If LGE indicated the presence of dead/fibrotic tissue, then we should have obtained a strong negative correlation with glucose uptake in this place, which would mean poor metabolism of fibrotic tissue. The lack of such association suggests diffuse interstitial fibrosis with potential local inflammation occurring rather typical replacement type.

Anderson et al. presented three different forms of cardiac fibrosis: reactive (interstitial) preserving cardiac structure and function; perivascular and replacement fibrosis and suggested that after the period of reactive interstitial fibrosis (while the heart adapts to the hemodynamic changes), replacement fibrosis may initiate upon cardiomyocyte death [20]. It seems that in treated PAH patients with high PVR and mPAP, CMR LGE indicates dynamic interstitial type of cardiac fibrosis. Thus, simple presence of LGE in RVIPs should not be unequivocal to inactive, necrotic tissue in this group of patients.

Limitations

This is an observational, pilot study with relatively small sample size but with two PET / MRI sessions during 24 months follow-up. T1 mapping by CMR (especially combined with ECV and T2 STIR) might have improved understanding of the fibrosis processes.

Conclusions

We show that LGE in RVIPs of PAH is metabolically active. This observed discrepancy opens

the way to further research based on development of inflammatory and fibrotic changes in myocardium of PAH patients.

Article information

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Conflict of interest None declared

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Table 1 Basic characteristics of pulmonary arterial hypertension (PAH) group at baseline and follow-up visit (after 24 months). Initial number of study group was 28 patients. During observation there were 4 deaths; 4 patients did not agree to participate in the follow-up visits.

	Baseline	**Follow-up**	***P* value**
Subjects, n	20[a]	20	-
CEP (deaths)	-	16 (4)	-
Sex (females), % (n)	75 (15)	70 (14)	-
Age, years	47.9±15.1	49.3±15.2	0.01
WHO Class	2.1 (0.7)	2.3 (0.7)	0.76
6 min walking test distance, m	404 (87.8)	412±77	0.15
BNP, pg/ml	90.8 [46–282]	114 [77–245]	0.14
PAH etiology			
Idiopathic / heritable PAH, % (n)	60 (12)	60 (12)	-
Connective tissue disease related PAH, % (n)	15 (3)	15 (3)	-
Congenital heart disease related PAH, % (n)	25 (5)	25 (5)	-
PAH specific therapy			
Phosphodiesteraze type 5 inhibitors, % (n)	40 (8)	10 (2)	-
Endothelin receptor antagonists, %	15 (3)	15 (3)	-

(n)			
Prostacyclins, % (n)	20 (5)	65 (13)	-
Phosphodiesteraze type 5 inhibitors + endothelin receptor antagonists, % (n)	20 (4)	10 (2)	-
Hemodynamics			
Systolic pulmonary artery pressure, mm Hg	82.2 (29.2)	72.2 (24.2)	0.44
Diastolic pulmonary artery pressure, mm Hg	33.8 (14.3)	28.2 (13.9)	0.33
Mean pulmonary artery pressure, mm Hg	50.5 (18.3)	42.8 (18.6)	0.03
Pulmonary capillary wedge pressure, mm Hg	10.6 (2.5)	9.73 (3)	0.26
Pulmonary vascular resistance, Wood units	8.9 (5.7)	7.3 (4.7)	0.04
Cardiac index, L/min/m^2	2.5 (0.4)	2.9 (0.4)	0.04
Right atrium pressure, mm Hg	8.6 (3.6)	8.1 (5.3)	0.64
RV parameters (MRI)			
RV ejection fraction, %	45.1 (9.6)	52.4 (12.9)	0.01
RV EDV/BSA, mL/m^2	113.2 (24.5)	106 (27)	0.27
RV ESV/BSA, mL/m^2	62.7 (22.7)	50 (11)	0.10
RV mass/BSA, g/m^2	39.9 (13.9)	39.2 (14.6)	0.50
RV compacted myocardium thickness, mm	5.7 (1.5)	5.2 (1.3)	0.56

Pulmonary arterial compliance, mL/mm Hg	2.4 (1.8)	3.2 (2.4)	0.04
Right ventricle stroke work index, g*m*m^2/beat	20.6 (8.4)	18.2 (7.5)	0.44
LGE mass, g	5.4 [2.3–9.4]	6.3 [3.4–11.4]	0.27
Myocardial metabolism (PET)			
SUV_{RV}	2.6 [1.4–5.5]	3.92 [1.6–8.1]	0.46
SUV_{LV}	3.7 [2.2–6.6]	5.7 [4.8–8.9]	0.10
SUV_{RV}/SUV_{LV} ratio	0.9 [0.4–1.4]	0.6 [0.4–1.1]	0.19
SUV_{RVIPS}	6.33 [2.5–9.9]	5.18 [3.3–7.7]	0.16

Data presented as mean (SD) (normal distribution) or median [IQR] (non-normal distribution) or categorical values % (n) where indicated. The dependent samples t-test or Wilcoxon signed rank test was used to compare matched (baseline vs follow-up) values depending on the distribution)

a number of matched pairs of patients present at both baseline and follow-up visits

Abbreviations: BNP, B-type natriuretic peptide; BSA, body surface area; CEP, clinical end-point; EDV, end-diastolic volume; ESV, end-systolic volume; FU, follow-up; LGE, late gadolinium enhancement; LV, left ventricle; MRI, magnetic resonance imaging; PET, positron emission tomography; RV, right ventricle; RVIPs, right ventricle insertion points; SUV, standardized uptake value; WHO, World Health Organisation

Short title: Cardiac glucose uptake and fibrosis in pulmonary arterial hypertension