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Original Article

Impact of pulmonary perfusion defects by scintigraphy on pulmonary vascular resistances, functional capacity and right ventricular systolic function in patients with chronic thromboembolic pulmonary hypertension

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Abstract: Chronic thromboembolic pulmonary hypertension (CTEPH) is a major cause of chronic pulmonary hypertension leading to right heart failure and death. Ventilation/perfusion single photon emission computed tomography (V/Q SPECT) is the screening test of choice showing mismatch in at least one segment or two sub-segments. Our aim was to investigate the relationship between the extent of pulmonary perfusion defects and hemodynamic, echocardiographic, biological and functional parameters. Between 2012 and 2019, 46 patients with CTEPH were retrospectively enrolled in the study. The diagnosis of pulmonary hypertension was made by the referral team of the expert center according to the European guidelines. All patients underwent pulmonary V/Q SPECT, right heart catheterization, transthoracic echocardiography (TTE), functional tests and natriuretic peptides assays. There was a slight correlation between the extent of pulmonary perfusion defects and pulmonary vascular resistances (R=0.510, P < 0.001). However, there was no correlation between the extent of pulmonary perfusion defects and NYHA stage, NT-proBNP level, functional parameters (6 minutes-walk distance-6 MWD), right ventricular function assessed by TTE. Pulmonary perfusion defects extension by V/Q lung SPECT are correlated with pulmonary vascular resistances in CTEPH. However, it is not correlated with right ventricular function and functional parameters.

Keywords: Chronic thromboembolic pulmonary hypertension, pulmonary ventilation/perfusion single photon emission computed tomography, pulmonary vascular resistances

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is categorized as group 4 in the classification of pulmonary hypertension [1]. Its incidence is thought to be 4 per 1 million adults [2, 3] complicating about 3% of pulmonary embolisms at one year [4]. Although its exact pathophysiology is complex and poorly understood, residual organized clot remaining attached to the wall of the pulmonary vessels seems to be the cornerstone of the initial mechanism, leading to the remodeling of the vascular wall, decrease of vascular compliance and subsequent increase of the pulmonary vascular resistances (PVR) [5]. The final consequence is an increase in pulmonary arterial pressure, leading to right ventricular dysfunction and impairment of functional capacities [5, 6]. Consequently, CTEPH is a functional entity whose diagnosis is based on the detection of perfusion defects. Ventilation/perfusion (V/Q) lung single photon emission computed tomography (SPECT) is the reference diagnostic examination of CTPEH showing mismatch in at least one segment or two sub-segments [1]. V/Q lung SPECT can determine the extent of pulmonary perfusion defects expressed as a percentage of the total lung parenchyma [7]. However, the relation between pulmonary perfusion defects

by V/Q lung SPECT and PVR, and their impact on right ventricular (RV) function have never been described.

The aim of our study was to investigate the relationship between the extent of pulmonary perfusion defects by V/Q lung SPECT and hemodynamic, echocardiographic, biological and functional parameters.

Methods

Study population

Between 2012 and 2019, 46 consecutives patients with CTEPH were retrospectively enrolled in this observational study. The diagnosis of pulmonary hypertension was made by the referral team of the expert center according to the European Society of Cardiology and the European Respiratory Society guidelines [1].

All patients underwent V/Q lung SPECT, right heart catheterization (RHC) and transthoracic echocardiography (TTE) during the same in-hospital stay. All patients were informed on admission that their clinical data could be used for research purposes, and all gave their consent. The data were collected as part of routine clinical care, in accordance with the principles of the Declaration of Helsinki. In accordance with applicable standards in France, this study has received ethics committee approval from the French Data Protection Authority (CNIL n 2206723).

Ventilation-perfusion lung single photon emission tomography

Perfusion SPECT was performed in accordance with the guidelines of the European Association for Nuclear Medicine [7] with a dual-head hybrid gamma camera (Symbia T6, Siemens Healthcare, Erlangen, Germany) equipped with a low-energy high-resolution collimator, in the supine position, after intra venous administration of 150 MBq ^{99m}Tc-macroaggregated albumin (MAA, TechneScan LyoMAA®, Mallinckrodt Medical, Petten, The Netherlands).

Pulmonary SPECT included a perfusion SPECT study and ventilation SPECT study obtained simultaneously within 10 min (i.e., 60 projections of 10 s each per head over 180°). Perfusion studies were performed after intravenous injection of 150 MBq of ^{99m}Tc-macroaggregated albumin (Curium, Saclay, france) during 2 respiratory cycles. Ventilation scintigraphy was conducted during inhalation of ^{81m}Kr made at our institution, which was extracted from a ^{81}Rb-^{81m}Kr generator (Curium, Saclay, France). Both studies were performed simultaneously with medium-energy, high-resolution collimators,and acquired in a 128 × 128 matrix. If ^{81m}Kr was not available, Technegas (Curium, Saclay, France) ventilation scintigraphy was performed only in combination with ^{99m}Tc-MAA perfusion scanning. Inhalation and imaging occurred preferably in the sitting position. Acquisition was performed using the same projections as for ^{81m}Kr ventilation scintigraphy (LEHR collimator, 128 × 128 matrix) (**Figure 1**).

The extent of the disease was quantified in accordance with the EANM guidelines by a pair of two physicians (PP & DE) blinded of the other clinical, imaging and hemodynamic results by counting the number of segments and subsegments indicating mismatch between perfusion and ventilation, and expressed as a percentage of the total lung parenchyma (**Figure 2**).

Transthoracic echocardiography

Echocardiograms were performed by 3 experienced senior cardiologists using a commercially available ultrasound Vivid E9 system (GE Vingmed Ultrasound AS) with a 2.5-MHz transducer. Images were acquired in accordance with the guidelines of the American Society of Echocardiography, the European Society of Echocardiography [8]. A complete Doppler, M-mode, and 2-dimensional greyscale echocardiogram including the 3 standard apical views (4-, 3-, and 2-chambers views) was obtained for all patients. Offline image analysis was performed by a single experimented operator (DE) blinded of other clinical, imaging and hemodynamic results using the EchoPAC software V202 (GE Vingmed Ultrasound AS).

Right heart catheterization

A Swan-Ganz catheter was used for RHC. Pulmonary capillary wedge pressure (PCWP), PASP, pulmonary artery diastolic pressure, and mean pulmonary arterial pressure (mPAP) were measured. Cardiac output was calculated by thermodilution as a mean of 3 consecutive measurements not varying by > 10%. The PVR in Wood units was calculated using the equa-

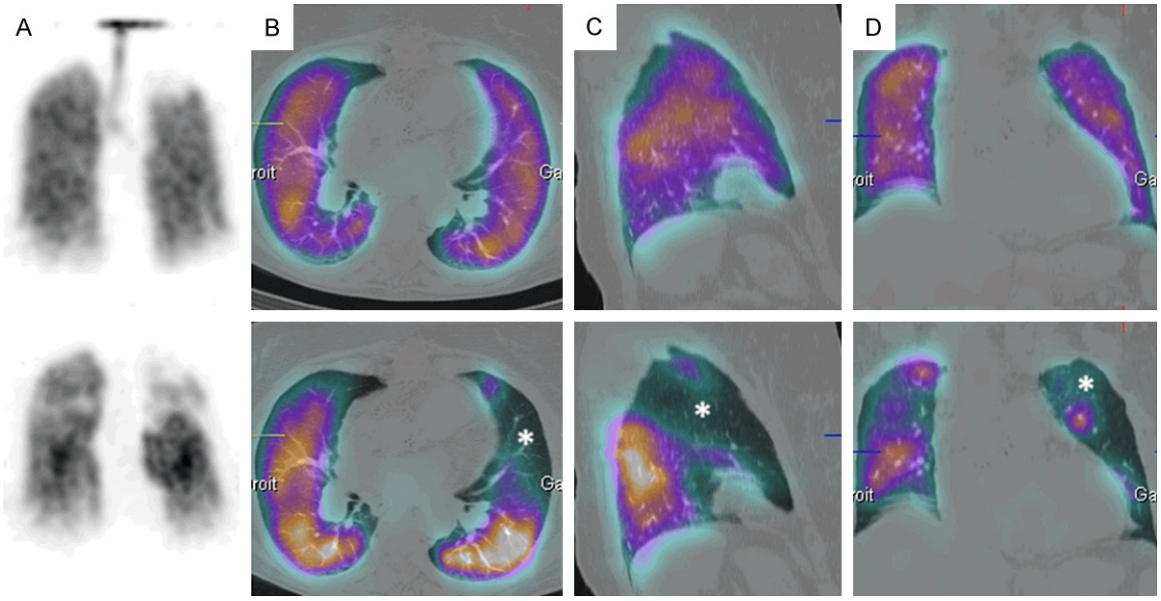

Figure 1. Ventilation/perfusion lung single photon emission computed tomography (V/Q SPECT) showing mismatch. Upper row: ventilation function; Lower row: perfusion function. (A) Planar acquisition; Computed tomography images in axial plane (B), sagittal plane (C) and coronal plane (D), mismatch are indicated with a *.

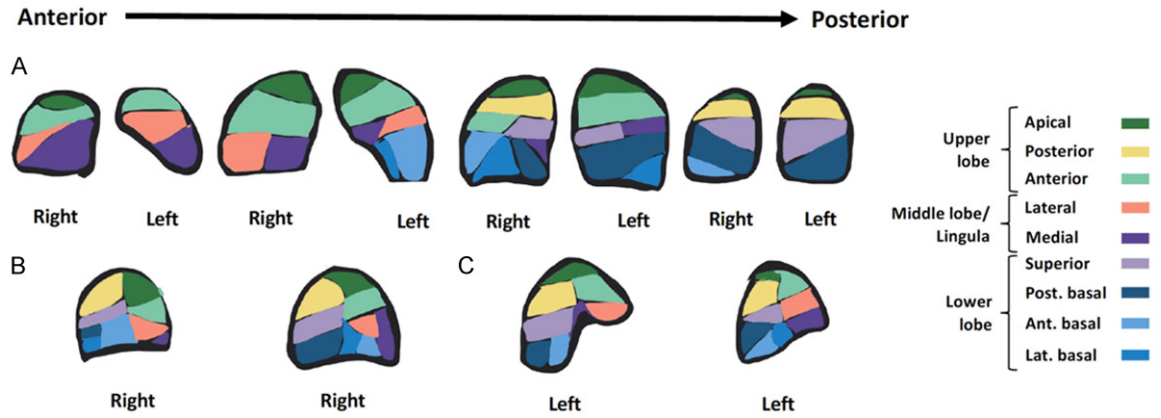

Figure 2. Pulmonary segmental map. A: Coronal slices anterior to posterior; B: Sagittal slices of right lung; C: Sagittal Slices of left lung.

tion: PVR = (mPAP-PCWP)/cardiac output. The pulmonary total resistances in dynes was calculated using the equation: pulmonary total resistances = (mPAP*80)/cardiac output.

Statistical analysis

Continuous variables were expressed with means ± standard deviation for normally distributed variables and medians and interquartile ranges for non-normally distributed variables. Nominal variables were expressed as number and percentages. Correlations between continuous variables were assessed using Spearman's correlation. All analyses were performed using standard statistical software SPSS version 20 (SPSS Inc., Chicago, Illinois).

Results

Population characteristics

The study population consisted of 46 patients whose characteristics are summarized in **Table 1**. Mean age was 66±16 years. There were 26 (57%) women.

Table 1. Population characteristics, echocardiographic and invasive findings

Demographic data	
Age, yrs	66±16
Female, n (%)	26 (56)
NYHA, n (%)	
NYHA I	3 (6)
NYHA II	17 (37)
NYHA III	21 (46)
NYHA IV	5 (11)
6 MWD, m	366±136
Biology	
NT-proBNP, pg/mL	1515 [246-3740]
Creatinine, umol/L	98±36
SPECT	
Defect, number of segment, n	9±4
Defect, percentage of lung parenchyma, %	48±20
Echocardiographic	
Left ventricular ejection fraction, %	60±8
LVEDD, mm	42±9
Tricuspid regurgitation velocity, m/s	4.0±0.5
Right atrial pressure, mmHg	8±4
PASP, mmHg	74±21
TVI_{RVOT}	11±5
Pulmonary acceleration time, ms	57±24
TAPSE, mm	18±5
Tricuspid annular S wave, m/s	11±3
Right ventricule area, cm^2	28±10
RV/LV index	1.1±0.3
RVEDD, mm	45±8
Fractional area change of RV, %	31±11
Right heart catheterization	
PVR, woods units	8.2±4.1
Pulmonary total resistances, dynes	810±450
mPAP, mmHg	41±10
PASP, mmHg	69±20
PCWP, mmHg	9±4
Cardiac output, L/min	4.1±1.2
Cardiac index, L/min/m^2	2.3±0.6
Right atrial pressure, mmHg	7±4

NYHA: New York Heart Association; 6 MWD: 6 minutes-walk distance; GFR: glomerular filtration rate; SPECT: single photon emission computed tomography; LVEDD: left ventricular end diastolic diameter; PASP: pulmonary artery systolic pressure; TVI_{RVOT}: time velocity integral of the right ventricular outflow tract; TAPSE: tricuspid annular plane systolic excursion; RV/LV: right ventricle/left ventricule; RVEDD: right ventricle end diastolic diameter; PVR: pulmonary vascular resistance; mPAP: mean pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure.

Almost all patients (97%) were symptomatic and reported dyspnea, with 26 (57%) patients New York Heart Association stage III or IV. The 6 minutes-walk distance (6 MWD) was 366±166 meters. The average NT-proBNP level was 1515 [246-3740] pg/mL.

Pulmonary perfusion defects quantified on V/Q lung SPECT was 9±4 expressed as a number of affected segments or 48±20% expressed as a percentage of the total lung parenchyma.

The TRV was 4.0±0.5 m/s allowing to estimate the PASP at 74±21 mmHg. The right ventricles were dilated with a mean RV end-diastolic diameter of 45±8 mm and a right ventricle/left ventricle index at 1.1±0.3 with preserved systolic function (TAPSE 18±5 mm, tricuspid annular S wave 11±3 cm/s) and preserved cardiac output (time velocity integral 11±5 cm).

Measurements of RHC found 41±10 mmHg of mPAP with a preserved cardiac output at 4.1±1.2 L/min (i.e. cardiac index 2.3±0.6 L/min/m^2) and therefore mean PVR calculated at 8.2±4.1 woods units and pulmonary total resistances at 810±450 dynes.

Correlations

Pulmonary perfusion defects measured by V/Q lung SPECT (expressed as a percentage of lung parenchyma) (**Table 2**) (R=0.510, P < 0.001; **Figure 3**). There was a correlation between pulmonary perfusion defects and mPAP measured by RHC (**Table 2**).

Furthermore, there was no correlation between pulmonary perfusion defects or RHC hemodynamic measurements and right ventricular function assessed in TTE (R=0.723, P=0.44 and R=0.59, P=0.44 with tricuspid annular plane excursion and S wave respectively). There was also no correlation between pulmonary perfusion defects or RHC hemodynamic measurements and the functional parameters estimated by the 6 MWD and New York Heart Association stage (data not shown).

Table 2. Correlation between SPECT, hemodynamics, TTE and functional parameters

	PVR		mPAP by RHC		PASP by TTE	
Pulmonary perfusion defect extension	R	P	R	P	R	P
	0.510	< 0.001	0.379	0.009	0.37	0.011
	6 MWD		NYHA III or IV		NT-proBNP	
Pulmonary perfusion defect extension	R	P	R	P	R	P
	0.10	0.956	-0.065	0.667	-0.148	0.336

PVR: pulmonary vascular resistances; mPAP: mean pulmonary arterial pressure; RHC: right heart catheterization; TAPSE: TAPSE: tricuspid annular plane systolic excursion; 6 MWD: 6 minutes-walk distance; NYHA: New York Heart Association.

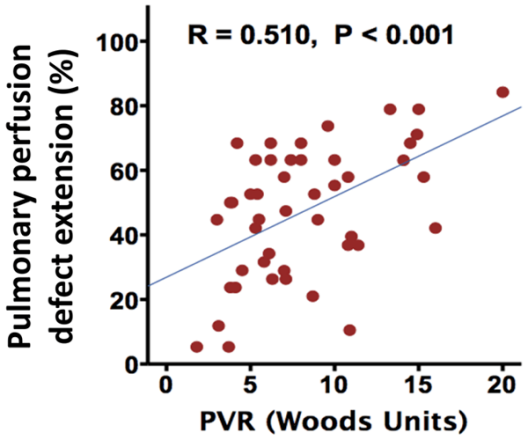

Figure 3. Correlation between pulmonary perfusion defects extension assessed in V/Q lung SPECT and pulmonary vascular resistance assessed by right heart catheterization. PVR: pulmonary vascular resistance.

Discussion

Our study shows that pulmonary perfusion defects quantified by V/Q lung SPECT correlate with PVR and pulmonary arterial pressures measured by RHC or TTE. However, we show that alteration of RV systolic function is associated with impaired functional capacities.

Azarian *et al.* had failed to demonstrate the existence of a correlation between pulmonary perfusion defects and PVR with lung perfusion scans [9]; the contribution of lung SPECT to the planar lung scans may explain this difference in results thanks to its better spatial resolution allowing a better quantification of the defects. The correlation between the extend of pulmonary perfusion defects and the increase in PVR is coherent insofar as we know that the initial element of the pathophysiology of CTEPH is a residual organized clot remaining attached to the walls of the pulmonary vessels [5]. Nevertheless, the correlation is slight in CTEPH and not good as Azarian *et al.* have described in the context of acute pulmonary embolism [9]. This is consistent and supported by the fact that there are other parameters independent of the obstruction involved in PVR. Indeed, over time, CTEPH becomes a disease of the small arteries following remodeling evolving on its own account and the impact of vasculopathy on pulmonary vascular resistances is increasing [10, 11].

Pulmonary perfusion defects extension data do not appear to be correlated to RV systolic function by TTE, to biological parameters or functional capacities. We can assume time an impact on RV remodeling: acute pulmonary hypertension does not give the same functional impact on the RV systolic functions as chronic pulmonary hypertension. Consequently, the defect itself does not prejudge the time the right ventricle has had to adapt. The adaptive changes can maintain RV systolic functions for a time, but the RV is not capable of sustaining long-term pressure overload [12]. Progressive dysfunction ensues, ultimately resulting in RV failure, which is then responsible for the decrease in functional capacities and can go as far as death [13].

Right heart catheterization is mandatory for hemodynamic evaluation; indeed the guidelines recommend a complete hemodynamic including cardiac output [1, 14] because PVR is important to assess diagnosis, prognosis and risks associated with pulmonary endarterectomy [15]. To date, non-invasive techniques are not efficient enough to offer a reliable hemodynamic evaluation. V/Q lung is the standard diagnostic test for CTEPH; the assessment of pulmonary perfusion defect extension by V/Q lung SPECT is easy and feasible in current practice and appears to correlate with hemodynamic assessment. V/Q lung SPECT does not provide an accurate hemodynamic

assessment but appears to correlate well with it.

Given the tendency to reduce invasive procedures, particularly in risk stratification [16], it would be interesting to know whether the pulmonary perfusion defects extension correlates with eligibility for pulmonary endarterectomy surgery or pulmonary angioplasty; similarly, it would be interesting to follow its evolution of and its correlation with hemodynamics after such procedures.

Limitations

Our study has all the limitations associated with retrospective, single-site and limited sample studies. Therefore our study may lack power; indeed we do not find correlations between hemodynamic parameters measured in RHC and right ventricular function in TTE or functional parameters what some have managed to demonstrated in literature. The lack of correlation between pulmonary perfusion defects and all these parameters is thus perhaps also due to his bias.

Finally, V/Q SPECT was performed when the disease was diagnosed but the delay between the onset of symptoms was unknown and probably variable.

Conclusion

In addition to its contribution to the diagnosis of CTEPH, pulmonary perfusion defects assessed by V/Q lung SPECT are correlated with pulmonary vascular resistances in CTEPH. However, it is not correlated with right ventricular function and functional parameters.

Disclosure of conflict of interest

None.

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