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Quantitative measurement of total lung vascular volume by computed tomography in COPD patients: correlation with clinical events and biological data

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Année : 2018

**MESURE QUANTITATIVE DU VOLUME VASCULAIRE PULMONAIRE
TOTAL PAR TOMODENSITOMETRIE CHEZ LES PATIENTS BPCO,
CORRELATION AVEC LES EVENEMENTS CLINIQUES ET LES
DONNEES BIOLOGIQUES**

THÈSE
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE
DIPLOME D'ÉTAT

Cevdet OZCELIK

[Données à caractère personnel]

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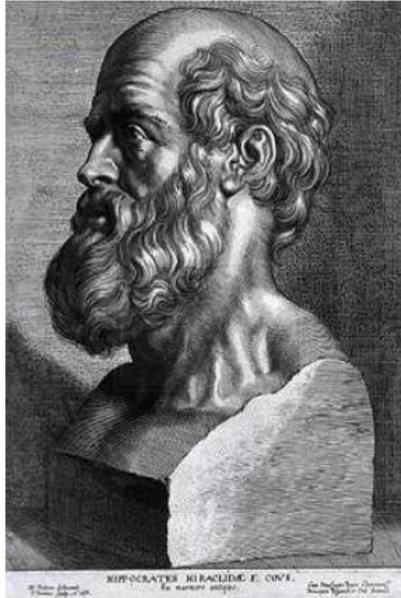
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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

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Liste des abréviations

ABPM: Ambulatory Blood Pressure Monitoring

COPD: Chronic obstructive pulmonary disease

CRP: C reactive protein

HsCRP: high sensitive C reactive protein

CT: computed tomography

FEV1: forced expiratory volume in one second

FVC: forced vital capacity

GOLD: global initiative for chronic obstructive lung disease

ICU : intensive care unit

IL 6 : inter-leukine 6

LVEF: left ventricular ejection fraction

MRI: magnetic resonance imaging

NoV: number of vessels

NoV5: number of vessels <5mm² cross section

Nt-pro-BNP: N-terminal pro-brain natriuretic peptide

Pa O²: pressure of artery oxygen

PFT: pulmonary function test

PH: pulmonary hypertension

TVV: total lung vascular volume

TVVn: normalised total lung vascular volume

TNF α : tumor necrosis factor α

Résumé

OBJECTIF

L'objectif était d'étudier par tomodensitométrie la relation entre les mesures quantitatives vasculaires et les données cliniques, les marqueurs sanguins de l'inflammation et du stress oxydatif chez les patients BPCO (bronchite pulmonaire chronique obstructive).

MATÉRIELS ET MÉTHODES

Le volume vasculaire pulmonaire total (TVV), la TVV normalisée à la surface corporelle (TVVn), le nombre total de vaisseaux (NoV) et le nombre de vaisseaux dont la section transversale est inférieure à 5 mm² (NoV5) ont été mesurés avec un logiciel sur des tomodensitométries thoraciques non injectées. Notre cohorte comprenait 62 patients atteints de BPCO (63,8 ans [59 ; 69,6] ; 74 % d'hommes) dont la répartition était : GOLD I n=8 (12,9 %), GOLD II n=39 (62,9 %), GOLD III n=10 (16,1 %) et GOLD IV n=5 (8,1 %). Les données cliniques concernant l'hospitalisation toutes causes confondues, l'infection pulmonaire, l'exacerbation et l'hospitalisation en unité de soins intensifs ont été enregistrées jusqu'à 5 ans après la tomodensitométrie thoracique. La fonction pulmonaire respiratoire (EFR), les gaz du sang artériel et la protéine C réactive plasmatique haute sensibilité (hsCRP), le fibrinogène, les thiols et la capacité antioxydante sérique totale ont été mesurés.

RÉSULTATS

TVVn avait une corrélation significative avec l'infection pulmonaire (OR = 1,06[1,01 ; 1,12] p = 0,02) et l'hospitalisation (OR = 1,06[1,01 ; 1,12] p = 0,01), HsCRP (β = 3,12 (0,84) p = 0,001) et une corrélation inverse avec la capacité antioxydante sérique totale (β = -90,21 (41,38) p = 0,03). Il n'y avait aucune corrélation entre la NoV et la NoV5 et les données cliniques.

CONCLUSION

Notre étude suggère que les mesures quantitatives par tomodensitométrie, en particulier la TVVn, peuvent aider à prédire les complications cliniques chez les patients BPCO et méritent d'être étudiées davantage.

Abstract

OBJECTIVES

To investigate the relationship between quantitative CT measurements of pulmonary vessel volume and number with clinical outcome, serum biomarkers of inflammation and oxidative stress, and lung function, in COPD patients.

MATERIALS AND METHODS

Total lung vascular volume (TVV), TVV normalized to body surface area (TVVn), total number of vessels (NoV) and number of vessels <5 mm² cross section (NoV5) were measured using a custom software on unenhanced thoracic CT scans. Our cohort included 62 COPD patients (63.8 years [59 ; 69.6]; 74% male) with the following distribution: GOLD I n=8 (12.9%), GOLD II n=39 (62.9%), GOLD III n=10 (16.1%) and GOLD IV n=5 (8.1%). Clinical outcome data for all-cause hospitalization, lung infection, exacerbation, and intensive care unit hospitalization, were recorded up to 5 years following chest CT. Lung function, arterial blood gas and high sensitivity plasma C-reactive protein (hsCRP), fibrinogen, thiols and serum antioxidant capacity were measured.

RESULTS

TVVn significantly correlated with pulmonary infection (OR = 1.06 [1.01; 1.12] p = 0.02) and hospitalization (OR = 1.06 [1.01; 1.12] p = 0.01), HsCRP (β = 3.12 (0.84) p = 0.001) and inversely correlated with total serum antioxidant capacity (β = -90.21 (41.38) p = 0.03). There was no correlation between NoV and NoV5 with clinical outcome.

CONCLUSION

Our study suggests that quantitative CT measurements, particularly TVVn may help predict clinical outcome in COPD patients, and merit further investigation as a surrogate imaging biomarker.

QUANTITATIVE MEASUREMENT OF TOTAL LUNG VASCULAR VOLUME BY COMPUTED TOMOGRAPHY IN COPD PATIENTS: CORRELATION WITH CLINICAL EVENTS AND BIOMARKERS

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Keywords :

COPD

Total lung vascular volume

Vascular phenotype

Inflammation

Oxydative stress

Introduction

Chronic Obstructive Pulmonary Bronchitis (COPD) is a progressive and irreversible impairment of breathing capacity. It is one of the leading causes of global mortality [1]. Morphologically, COPD is characterized by both progressive parenchymal destruction leading to emphysema, and significant remodelling of small airways [2-3]

It is increasingly recognized that changes in pulmonary vasculature, which have been demonstrated by post-mortem morphological analysis on autopsy [4-5] as well as imaging study [6-7], may accompany or even precede emphysematous changes in the lung parenchyma. Such vascular lesions are manifested by a remodelling of the pulmonary arterioles through proliferation of smooth muscle cells and vasoconstriction in the early moderate stages of COPD [8]. Although such phenomena may occur as a result of alveolar hypoxia, and may lead to pulmonary hypertension with time and disease progression [9], other mechanisms such as oxidative stress due to both tobacco exposure and recruitment and activation of inflammatory cells in the lungs [10] or repeated exacerbations or lung infection may be involved [11].

CT imaging offers the possibility to quantitatively assess the pulmonary vasculature. Distal vascular changes have been documented in recent studies, demonstrating an inverse correlation between the cross-sectional surfaces of small pulmonary vessels and emphysema [12]. However, there are a proportion of COPD patients without correlation between emphysema and decreased cross-sectional area of small pulmonary vessels, involving other phenomena as endothelial dysfunction [13], suggesting different lesional phenotypes.

Currently, the significance of changes in pulmonary vascular morphology in COPD patients and whether they are associated with clinical outcome, such as exacerbation or hospitalization, is not known. In this study, we hypothesized that changes in pulmonary vascular morphology, namely

the total volume of the vascular network and the number of pulmonary vessels may be associated with clinical outcomes such as exacerbation, pulmonary infection, all-cause hospitalization or intensive care unit (ICU) hospitalization. We further assessed whether changes in morphologic indices of the pulmonary vascular tree were related to inflammation, oxidative stress, lung function and gas exchange.

Materials and methods

Study population

121 COPD patients selected from a cohort of COPD patients followed at the Grenoble University Hospital, were prospectively enrolled in the study.

The inclusion criteria for the initial cohort were : age > 18 years and FEV1/FVC <70%. Patients with ongoing infection or plasma CRP > 100 mg/l; acute decompensation of chronic heart failure or left ventricular ejection fraction (LVEF) < 45%; tobacco smoke exposure < 10 cigarettes/day; active neoplasia; antioxidant treatment (n-acetyl-cysteine, selenium, vitamin C or E); pregnancy or breastfeeding; inability to provide informed consent; participation in another clinical research study; lack of health insurance coverage; deprived of civil liberty or claustrophobia were excluded from the study.

All patients gave written informed consent. The study was a registered under AFSSAPS 2006-A00491-50.

Study design

During the clinical follow-up, clinical events were recorded up to 5 years after CT scan when possible. Those events were all-cause hospitalization, hospitalization in ICU, lung infection, and exacerbation. Lung infection and exacerbation have been diagnosed by the physician.

CT Imaging

All patients underwent chest CTs with the following protocol: 120kV, slice thickness 0,625 mm spaced by 0,625 mm intervals.

We used a custom thoracic vessel segmentation software developed by us (Broche L. 2017). The images were processed by a single radiologist with 5 years of experience (C.O). The pulmonary vasculature was segmented automatically as follows: vascular arterial or venous reference points were manually selected in the mediastinal window. Three points of reference were positioned in the upper, middle and lower third of each lung. The software then mapped the complete vascular system, including pulmonary arteries and veins using a region growing algorithm. Following segmentation, the total lung vascular volume (TVV) was computed and reported in ml. A 3D rendering of the segmented vessels was examined in order to ensure quality. The TVV was subsequently normalized to body surface area in order to account for between-subject differences in body size.

Additionally, the software provided the number of in-plane vessels observed in 3 reference axial slices selected in a standardized manner [12] : 1 cm above the aortic arch for the apical slice, 1 cm below the carina for the middle slice, and 1 cm below the lower right pulmonary vein for the caudal slice. Vessels oblique to the axial image plane were excluded in order to avoid overestimation of the cross-sectional area [14-15]. The total number of vessels (NoV) and the number of vessels with a cross section $< 5 \text{ mm}^2$ (NoV5) within the 3 slices were reported.

Emphysema was assessed using a commercial software (Software ADW 4.6 GE Healthcare, Milwaukee, WI, USA). An attenuation threshold of -950HU was selected according to previous studies in the literature [12-15]. Data were reported as percentage of lung total volume.

The diameters of the pulmonary artery trunk and the aorta were measured on the same section using manual calipers (Software ADW 4.6 GE Healthcare, Milwaukee, WI, USA).

Image processing

Images were processed with a custom made software based on the python programming language (Python Software Foundation; Python Language Reference, version 2.7). Segmentation of the aerated lung volume from the CT images was performed using a region growing algorithm [16] which include all voxel spatially connected with a density value ranging from -1023 to -224 HU. With a morphological operation the blood vessels and bronchi structures were included into the image mask (morphological closing with a 5 mm diameter sphere followed by an erosion with a 2 mm diameter sphere). Within the lung mask the blood vessels were extracted with an active contour segmentation [17] initialized by manually selected seeds points within the structure. The segmented vessels isosurfaces were smoothed by a Laplacian filter to remove potential pixelated effect.

Vessels number and surface were measured in three separate axial cross sections manually positioned (described above). Only vessels cross section going through the reference planes with a circularity higher than 0.8 were selected for measurement. Surface was computed by fitting the vessels contour with an ellipse.

Blood analysis

Blood biomarkers were collected: hsCRP, NT-pro-BNP, fibrinogen, protein, and blood gases.

Blood oxidative stress markers were evaluated by 2 biomarkers:

- Total serum antioxidant power (SAP) based on the reduction of a chromogenic sensitive to redox equilibrium plasma (Randox). This setting takes into account all the antioxidants and pro-oxidants plasma parameters and measures the antioxidant capacity of serum.

- Plasma thiols: colorimetric measurement thanks to a Hitachi automaton. Plasma thiols are essentially represented by those of the albumin, which is the most powerful extracellular antioxidant.

Lung function

Pulmonary function tests (PFT) were performed before or after the CT examinations. Lung function testing was performed using a BodyBox system (Medisoft, Sorinnes, BE). The forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, residual volume (RV), and total lung capacity (TLC) were recorded and expressed as percentage of predicted values.

Other physiological measurements were performed using: measurements of heart rate and transcutaneous oxygen saturation.

Statistical analysis

For the primary objective, we analysed the relationship between CT vascular parameters (TVV, TVVn, NoV and NoV5) and clinical events (all-cause hospitalization, ICU hospitalization, exacerbation, pulmonary infection).

For the secondary objective, we compared those same CT parameters to blood analysis parameters (hsCRP, Nt-pro-BNP, fibrinogen, plasma thiols, protein, thiols/protein ratio, serum antioxidant power, Pa O₂, Pa CO₂, blood pH, bicarbonates, IL6, TNF- α), GOLD stage and pulmonary functional tests.

Univariate analysis (primary and secondary objectives)

For quantitative variables, we used the Mann and Whitney or Kruskal-Wallis tests. For qualitative variables, Fisher exact test was used. A simple imputation was performed for missing data and replaced by the median for each categorical variable.

Multivariate analysis

For the selection of multivariate variables, we used a logistic regression step for each clinical events, thought 3 lists separately. The collinearity between the variables and the least collinear variables of the 3 lists were tested. Stepwise logistic regression for clinical group used the following variables: age, sex, total lung vascular volume (per 10 units), total vessels number.

Results

Population characteristics

Out of the 121 patients in the cohort, 47 patients were excluded for lack of as they did not have chest CT data at upon inclusion or during follow-up. Seventy four patients underwent chest CT imaging from April 2007 to January 2016. Blood samples were obtained inclusion.

The demographic, clinical, blood analysis and pulmonary function data of patients are shown in Table 1. Median age was 63.8 years [59 ; 69.6], with a body mass index of 25.8 kg/m² [21.1 ; 28.7], and tobacco smoking history of 40 pack-years [20 ; 53]. Disease severity based on the GOLD classification was as follows: GOLD I: 8%, GOLD II : 39%, GOLD III: 10%, and GOLD IV: 5%.

Data on the main outcome measures of the study are summarized in Table 2. Exacerbation was the most frequent adverse clinical outcome (51.6%) followed by all-cause hospitalisation (50%).

Primary objective: study of vascular parameters and clinical events of COPD patients

Univariate analysis

TVV and TVVn were significantly higher for hospitalized patients (375 ml [319,3 ; 481,6] vs 315 ml [228.5 ; 389.8], p=0.01) and (200.7 ml [180.3 ; 261.1] vs 165 ml [138.5 ;212.4], p= 0.02) respectively.

Concerning lung infections, TVV and TVVn significantly increased for patients who had lung infection (237.3 ml [187; 275.7] vs 185.2 ml [150.6; 212.4] $p = 0.05$) and 458 [345 ; 489.5] vs 339 ml [246.4 ; 389.8], $p=0.02$ respectively. .

There is no significant difference concerning TVV and TVVn for the other clinical event ($p>0.05$).

NoV and NoV5 didn't show any significant correlation with clinical events in our study ($p>0.05$).

Multivariate analysis

Multivariate analysis were performed for correlations with a univariate $p\leq 0.3$.

A stepwise logistic regression was used for each clinical events group with the variables: age, sex, total pulmonary vascular volume (per 10 units) and number of vessels.

The higher the TVVn, the higher was the risk of lung infections and hospitalization (respectively OR=1.06 $p=0.02$ and OR=1.06 $p=0.01$).

Secondary objective: relationships between lung vascular volume and biological data

Univariate analysis

TVVn was correlated to hsCRP (regression coefficient (β) =3.64 (0.89), $p = 0.01$), inversely correlated) to serum antioxidant power ($\beta=-102.77$ (48.03), $p = 0.036$) (table 5) and to blood oxygen saturation ($\beta =-10.22$ (5.01), $p = 0.046$) (Table 6).

There was no a significative correlation concerning the other serum biomarkers (blood PaO², fibrinogen, plasma tiols), nor respiratory functional data (Tiffeneau ratio, FEV1), nor morphological data (emphysema, pulmonary artery diameter/aortic diameter ratio) (Table 7).

Multivariate analysis

There was an inverse correlation of TVVn with oxygen saturation ($\beta = -9.44$ (3.46), $p = 0.01$), and with the total anti-oxidant power ($\beta = -90.21$ (41.38), $p = 0.03$).

There was a significant independent correlation between TVVn and hsCRP ($\beta = 3.12 (0.84)$ $p = 0.001$) (table 8).

Discussion

This study was undertaken to explore the relation between changes in pulmonary vascular morphology and 5-year post-CT clinical outcome in a cohort of patients with mild to moderate COPD. Our main findings were that body surface area-normalized total lung vascular volume (TVVn) was significantly correlated to all-cause hospitalisation and lung infection, as well as to some markers of systemic inflammation such as high-sensitivity CRP, while it was inversely correlated to total serum anti-oxidant capacity.

One of the most frequent co-morbidities of COPD is pulmonary vascular disease with a prevalence of pulmonary hypertension between 30% and 70 % [18]. However, the true prevalence of pulmonary hypertension in mild to moderate COPD is hard to estimate due to lack of large scale epidemiological studies and to the fact that pulmonary artery catheterisation is an invasive procedure. Moreover, up to two-thirds of COPD patients with normal resting pulmonary hemodynamics at rest may have abnormal pulmonary vascular pressure elevations during exercise [19]. When present, pulmonary hypertension is associated with exercise intolerance and increased risk of hospitalisation and mortality [20].

In the present study, we applied an automated analysis of lung CT images to measure the total volume of the segmented pulmonary vasculature. Our finding that an increased TVVn was associated with increased risk of lung infection and all-cause hospitalisation, may be explained by the progressive remodelling and increased resistance of small pulmonary arterioles, leading to

upstream distension of larger arterial branches. These larger more proximal vessels may have contributed more to the total vascular volume than the small peripheral vessels. The different mechanisms that may lead to increased arteriolar resistance, due to constriction and remodelling include hypoxemia and hypercapnia, polycythemia and acidosis, and mechanisms which lead to pruning of the vascular tree, comprising lung parenchymal destruction due to emphysema and inflammation related to cigarette smoke exposure and recurrent lung infections [18, 20]. In the present study, systemic inflammation as reflected by high sensitivity CRP and a decreased blood antioxidant capacity were significantly correlated with TVVn, while the estimated number of small pulmonary vessels was significantly correlated only with high-sensitivity CRP (Table 5). We found no significant correlation between lung vascular measurements and neither lung functional nor gas exchange parameters, emphysematous changes in the parenchyma as quantified by LAA%, nor AP/Ao ratio.

Previous studies have found that extra parenchymal vascular engorgement as assessed by a AP/Ao ratio > 1 is associated with severe exacerbations of COPD [21]. However, a single measurement of the pulmonary arterial trunk may be less sensitive to changes in the total volume of the pulmonary vasculature measured in 3D [22-23], which may explain the lack of significant correlation between this metric and TVV in the present study.

We did not find a significant correlation between the number of small pulmonary vessels and clinical outcome. Several previous studies have found that a 2-dimensional measurement of small vessel cross-sections ($\%CSA < 5 \text{ mm}^2$) expressed as percentage of the total lung cross section significantly correlates negatively with emphysema and positively with FEV1 [24-12] as well as with acute COPD exacerbation [25]. One hypothesis is that in our population of mild to moderate COPD patients, remodelling of the peripheral pulmonary blood vessels may have been the predominant mechanism rather than pruning of the vessels due to parenchymal destruction and

emphysema. Another potential explanation is that our study included only a small number of severe COPD patients (GOLD IV 8%) similar to the overall COPD population [26] and the prevalence of pulmonary vascular remodelling and hypertension may have been limited in these patients. Moreover, %CSA $< 5 \text{ mm}^2$ reported in previous studies in the literature is an aggregate metric which may be driven both by the cross-section of small vessels as well as the cross-sectional area of the lung. The latter may be significantly affected by hyperinflation and emphysema, which may explain the strong correlations between this parameter and %LAA in other studies. This may explain why some studies have failed to find a consistent relation between %CSA $< 5 \text{ mm}^2$ and %LAA in all COPD patients [15].

We found a significant correlation between TVVn and systemic inflammation (HsCRP) as well as an inverse correlation with total serum anti-oxidant capacity, a marker of coping mechanisms against oxidative stress. The oxidative stress produced by tobacco smoke exposure is thought to have a central role in COPD progression [27]. Inflammation is believed to be partly responsible for vascular endothelial dysfunction resulting in vasoconstriction and proliferation of endothelial smooth muscle cells leading to pulmonary vascular remodelling and pruning. Systemic inflammation and oxidative stress are also thought to play a significant role in cardiovascular comorbidities [28-29], neurodegenerative diseases [30-31], metabolic syndrome [32-33], cancer [34] in COPD patients. Inflammation and oxidative stress are also closely associated with lung infection [10], and may therefore represent pathways through which patients with increased risk of hospitalisation and lung infection may be characterized by an increase in TVVn.

According to our study, vascular parameters were independent to other historical CT phenotypes data for COPD patients such as emphysema ($\beta = 0.64 (0.72)$, $p=0.379$) or FEV1 ($\beta = -0.48 (0.4)$, $p=0.241$). Vascular parameters may therefore be a key factor to take into account in COPD patients, although this observation remains to be confirmed by a larger scale prospective study.

Our study had several limitations. First, this was a retrospective observational study on a small population of mainly mild to moderate COPD patients. Our study would have benefited from the inclusion of healthy controls and smokers without COPD in order to better characterize the natural history of the changes in pulmonary vascular morphology. Moreover, the natural variations in pulmonary vasculature are currently unknown in healthy subjects. It would be therefore interesting to complete this study by conducting comparative studies of TVVn in healthy subjects, smokers without obstructive disease (stage 0 COPD) and smokers with COPD, in order to investigate vascular disease phenotypes in smokers with or without COPD. The metric used for the assessment of small pulmonary vessels included only the number of vessels with a cross-section $< 5 \text{ mm}^2$. Although this measure is relevant to pruning of the pulmonary vasculature, the total cross-section of small vessels normalized to the total vascular volume could potentially have better characterized pulmonary vascular remodelling.

Conclusion

We investigated the relationship between changes in pulmonary vascular morphology and 5-year post-CT clinical outcome in a cohort of patients with mild to moderate COPD. Our data show that TVVn is associated with a small but significant additional risk of lung infection and all-cause hospitalization, is correlated to high-sensitivity CRP, a marker of systemic inflammation, and is inversely correlated to total serum antioxidant capacity. Moreover, the number of small pulmonary blood vessels was significantly correlated to hsCRP highlighting the role of systemic inflammation in the pruning of the peripheral pulmonary vasculature. Together, these data suggest that the non-invasive quantitative assessment of the pulmonary vasculature by multi-detector CT imaging may help characterize patient phenotypes at risk of infection and hospitalization, and merits larger controlled studies.

Figures and tables

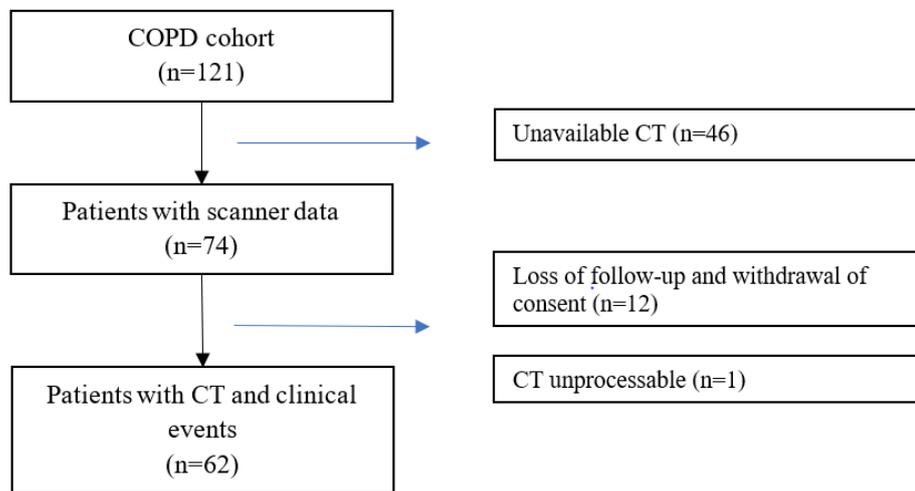


Figure 1: Flowchart of the cohort

Variables	Items	n (%) ; median [Q1 ; Q3]	Missing (%)
Age (years)		63.8 [59 ; 69.6]	
Sex	male	46 (74.2)	
Body mass index (kg/m ²)		25.8 [21.1 ; 28.7]	
Tabacco pack-year		40 [20 ; 53]	1 (1.6)
Diabetes		7 (11.3)	
High blood pressure ABPM 24h >130/80mmHg		30 (48.4)	
Dyslipidaemia		27 (43.5)	
HsCRP (if normal CRP) (mg/l)		2.8 [1 ; 7.4]	2 (3.2)
Fibrinogen (g/l)		3.6 [3 ; 4.1]	
COPD Stage	GOLD 1	8 (12.9)	
	GOLD 2	39 (62.9)	
	GOLD 3	10 (16.1)	
	GOLD 4	5 (8.1)	
Heart failure (None)		61 (100)	1 (1.6)
Nt pro BNP (pg/mL)		71.5 [40 ; 125]	
IL6 (UI)		7 [2 ; 19]	37 (59.7)
TNFa (UI)		10 [2 ; 10]	37 (59.7)
Emphysema (-950UH, %)		9.5 [2.3 ; 16.5]	1 (1.6)
Plasma thiols (UI)		423 [394 ; 455]	

Qualitative variables are presented in number and percentage (n (%)) and quantitative variables in median and interquartile range.

Table 1: Population characteristics

Variables	n (%)
Exacerbation	32 (51.6)
All-cause hospitalization	31 (50)
Lung infection	13 (21)
ICU hospitalization	7 (11.3)

Lung infection and exacerbation have been diagnosed by the physician.
All-cause hospitalization and all-cause ICU hospitalization

Table 2: Clinical events

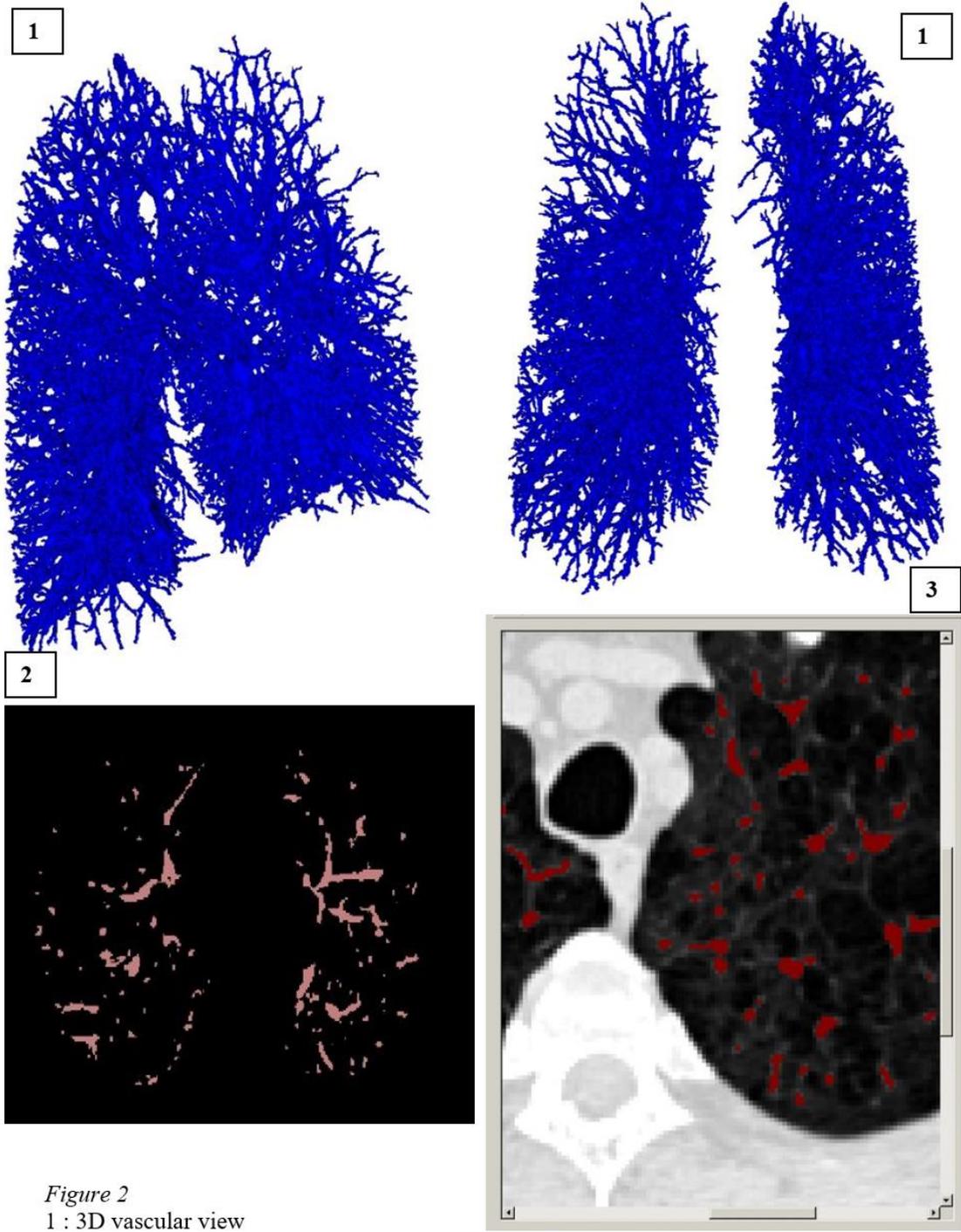


Figure 2
1 : 3D vascular view
2 : axial view vascular
reconstruction
3 : axial view vascular and CT

Variable	All-cause hospitalization			ICU hospitalization			Exacerbation			Lung infection		
	No (n=31)	Yes (n=31)	p	No (n=49)	Yes (n=13)	p	No (n=30)	Yes (n=32)	p	No (n=55)	Yes (n=7)	p
TVV ml	315 [228.5 ; 389.8]	375 [319.3 ; 481.6]	0.01	347 [268 ; 418.9]	375 [258.5 ; 398]	0.67	367.5 [246.3 ; 392.6]	340.5 [279.3 ; 438.5]	0.93	339 [246.4 ; 389.8]	458 [345 ; 489.5]	0.02
TVVn ml	165.8 [138.5 ; 212.4]	200.7 [180.3 ; 261.1]	0.02	189 [155.5 ; 231.9]	200.7 [152.3 ; 261.1]	0.66	191.4 [155.7 ; 231.9]	188 [153.9 ; 242.2]	0.83	185.2 [150.6 ; 212.4]	237.3 [187 ; 275.7]	0.05
NoV	39 [33 ; 52]	46 [39 ; 61]	0.13	46 [34 ; 55]	42 [37 ; 56]	0.81	45.5 [35 ; 52]	45 [35.5 ; 59.5]	0.68	43 [35 ; 52]	54 [42 ; 62]	0.09
NoV5	32 [25 ; 46]	39 [35 ; 47]	0.14	38 [27 ; 46]	37 [29 ; 45]	1.00	38.5 [29 ; 46]	37.5 [28.5 ; 46.5]	0.94	37 [29 ; 44]	45 [37 ; 52]	0.16

Quantitative values were presented as follow : median [Q1 ;Q3]
The Mann and Whitney or Kruskal-Wallis tests used

Table 3: Correlation between vascular parameters (TVV, TVVn, NoV, NoV5) and all-cause hospitalisation, exacerbation, ICU hospitalization, and lung infection.

Clinical events	Variable	OR [IC]	p
Lung infection	TVVn (per 10 units)	1.06[1.01 ; 1.12]	0.02
All-cause hospitalization	TVVn (per 10 units)	1.06[1.01 ; 1.12]	0.01

Table 4: Multivariate study of TVVn and lung infection and all-cause hospitalization

Variable	items	TVVn		NoV		Nov5	
		β^1 (SE)	p	β^1 (SE)	p	β^1 (SE)	p
hsCRP		3.64 (0.89)	<0.001	0.79 (0.25)	0.002	0.44 (0.21)	0.04
Nt pro BNP		0.04 (0.02)	0.043	0.01 (0)	0.253	0.01 (0)	0.142
Fibrinogen		7.5 (9.84)	0.449	3.49 (2.61)	0.186	1.03 (2.12)	0.628
Plasma thiols		-0.23 (0.15)	0.144	-0.03 (0.04)	0.443	-0.04 (0.03)	0.212
Protein		-1.56 (1.12)	0.171	-0.19 (0.3)	0.543	-0.13 (0.24)	0.587
Thiols/protein ratio		-6.51 (12.57)	0.606	-1.35 (3.37)	0.69	-2.82 (2.69)	0.298
Total antioxidant serum power		-102.77 (48.03)	0.036	-14.87 (13.22)	0.265	-7.01 (10.68)	0.514
PaO ₂		-2.02 (1.06)	0.062	0.05 (0.29)	0.852	-0.12 (0.23)	0.621
PaCO ₂		0.26 (2.04)	0.897	0.13 (0.55)	0.818	-0.2 (0.44)	0.654
pH		-86.72 (340.73)	0.80	-34.93 (91.28)	0.703	-32.48 (73.23)	0.659
Bicarbonates		-0.41 (2.14)	0.85	-0.26 (0.57)	0.658	-0.34 (0.46)	0.46

¹: correlation factor β : increase of one unit of variable is associated with increase in the TVVn

Table 5: correlation between vascular parameters (TVVn, NoV, NoV5) with biomarkers

Variable	items	TVVn		NoV		Nov5	
		β^1 (SE)	p	β^1 (SE)	p	β^1 (SE)	p
Saturation		-10.22 (5.01)	0.046	-0.12 (1.39)	0.931	-1.22 (1.1)	0.271
FEV1		-0.48 (0.4)	0.241	0.03 (0.11)	0.786	0.08 (0.09)	0.353
FVC		-0.41 (0.4)	0.304	0.02 (0.11)	0.853	0.01 (0.09)	0.886
FEV1/FVC (Tiffeneau ratio)		-0.69 (0.66)	0.299	0.06 (0.18)	0.744	0.16 (0.14)	0.268
VC		-0.26 (0.46)	0.571	0.01 (0.12)	0.928	0.06 (0.1)	0.547
IC		-0.61 (0.35)	0.086	-0.15 (0.09)	0.106	-0.07 (0.08)	0.386
TLC		-0.06 (0.47)	0.904	-0.27 (0.12)	0.027	-0.19 (0.1)	0.06

¹: correlation factor β : increase of one unit of variable is associated with increase in the TVVn

Table 6: correlation between vascular parameters (TVVn, NoV, NoV5) with functional data (PFT)

Variable	items	TVVn		NoV		Nov5	
		β^1 (SE)	p	β^1 (SE)	p	β^1 (SE)	p
Emphysema (-950UH)		0.64 (0.72)	0.379	-0.03 (0.2)	0.896	-0.18 (0.16)	0.255
PA diameter (mm)		1.37 (1.88)	0.47	-0.14 (0.51)	0.789	0.27 (0.41)	0.509
PA/Ao ratio ²		29.73 (69.54)	0.671	1.85 (18.67)	0.921	10.64 (14.92)	0.478

¹ : correlation factor β : increase of one unit of variable is associated with increase in the TVVn

² : pulmonary artery diameter/aorta diameter ratio

Table 7: correlation between vascular parameters (TVVn, NoV, NoV5) with CT morphological data

TVVn			
Variables	β (SE)	P	Variables used in the model
HsCRP	3.12 (0.84)	0.001	IC, hsCRP, Nt pro BNP, anti-oxidant serum power, Protein, O ² Saturation, FEV1/FVC ratio.
O² saturation	-9.44 (3.46)	0.01	
Total anti-oxidant serum power	-90.21 (41.38)	0.03	

Table 8: Multivariate correlation between vascular volume and biological data

References

- [1] Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 15 Feb 2013;187(4):347–65.
- [2] Petty TL. Building a National Strategy for the Prevention and Management of and Research in Chronic Obstructive Pulmonary Disease. National Heart, Lung, and Blood Institute Workshop Summary. *JAMA: The Journal of the American Medical Association*. 1997 Jan 15;277(3):246.
- [3] McDonough JE, Yuan R, Suzuki M, Seyednejad N, Elliott WM, Sanchez PG, et al. Small-Airway Obstruction and Emphysema in Chronic Obstructive Pulmonary Disease. *New England Journal of Medicine*. 2011 Oct 27;365(17):1567–75.
- [4] Magee F, Wright JL, Wiggs BR, Paré PD, Hogg JC. Pulmonary vascular structure and function in chronic obstructive pulmonary disease. *Thorax*. 1 Mar 1988;43(3):183–9.
- [5] Santos S, Peinado VI, Ramírez J, Melgosa T, Roca J, Rodriguez-Roisin R, et al. Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD. *European Respiratory Journal*. 1 Apr 2002;19(4):632–8.
- [6] Alford SK, van Beek EJR, McLennan G, Hoffman EA. Heterogeneity of pulmonary perfusion as a mechanistic image-based phenotype in emphysema susceptible smokers. *Proceedings of the National Academy of Sciences*. 2010 Apr 20;107(16):7485–90.
- [7] Estépar RSJ, Kinney GL, Black-Shinn JL, Bowler RP, Kindlmann GL, Ross JC, et al. Computed Tomographic Measures of Pulmonary Vascular Morphology in Smokers and Their Clinical Implications. *American Journal of Respiratory and Critical Care Medicine*. 2013 Jul 15;188(2):231–9.
- [8] Barberà JA, Peinado VI, Santos S. Pulmonary hypertension in chronic obstructive pulmonary disease. *European Respiratory Journal*. May 2003;21(5):892–905.
- [9] Naeije R, Barberà JA. Pulmonary hypertension associated with COPD. 2001;5(6):4.
- [10] Repine JE, Bast A, Lankhorst I. Oxidative Stress in Chronic Obstructive Pulmonary Disease. 1997;156:17.
- [11] Mallia P. Mechanisms and Experimental Models of Chronic Obstructive Pulmonary Disease Exacerbations. *Proceedings of the American Thoracic Society*. 2005 Nov 1;2(4):361–6.
- [12] Matsuoka S, Washko GR, Dransfield MT, Yamashiro T, San Jose Estepar R, Diaz A, et al. Quantitative CT Measurement of Cross-sectional Area of Small Pulmonary Vessel in COPD. *Academic Radiology*. Jan 2010;17(1):93–9.
- [13] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for Chamber Quantification: A Report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification

Writing Group, Developed in Conjunction with the European Association of Echocardiography, a Branch of the European Society of Cardiology. *Journal of the American Society of Echocardiography*. 2005 Dec;18(12):1440–63.

[14] Coste F, Dournes G, Dromer C, Blanchard E, Freund-Michel V, Girodet P-O, et al. CT evaluation of small pulmonary vessels area in patients with COPD with severe pulmonary hypertension. *Thorax*. sept 2016;71(9):830–7.

[15] Mashimo S, Chubachi S, Tsutsumi A, Kameyama N, Sasaki M, Jinzaki M, et al. Relationship between diminution of small pulmonary vessels and emphysema in chronic obstructive pulmonary disease. *Clinical Imaging*. nov 2017;46:85–90.

[16] Kybic J, Unser M: Fast parametric elastic image registration. *IEEE transactions on image processing* : a publication of the IEEE Signal Processing Society 2003, 12(11):1427-1442.

[17] Leventon, M.E. et al. "Statistical Shape Influence in Geodesic Active Contours", *CVPR 2000*

[18] O.A. Minai, A. Chaouat, S. Adnot, Pulmonary hypertension in COPD: epidemiology, significance, and management: pulmonary vascular disease: the global perspective, *Chest* 137(6 Suppl) (2010) 39S-51S.

[19] M. Oswald-Mammoser, M. Apprill, P. Bachez, M. Ehrhart, E. Weitzenblum, Pulmonary hemodynamics in chronic obstructive pulmonary disease of the emphysematous type, *Respiration; international review of thoracic diseases* 58(5-6) (1991) 304-10.

[20] F.N. Rahaghi, E.J. van Beek, G.R. Washko, Cardiopulmonary coupling in chronic obstructive pulmonary disease: the role of imaging, *J Thorac Imaging* 29(2) (2014) 80-91.

[21] J.M. Wells, G.R. Washko, M.K. Han, N. Abbas, H. Nath, A.J. Mamary, E. Regan, W.C. Bailey, F.J. Martinez, E. Westfall, T.H. Beaty, D. Curran-Everett, J.L. Curtis, J.E. Hokanson, D.A. Lynch, B.J. Make, J.D. Crapo, E.K. Silverman, R.P. Bowler, M.T. Dransfield, C.O. Investigators, E.S. Investigators, Pulmonary arterial enlargement and acute exacerbations of COPD, *The New England journal of medicine* 367(10) (2012) 913-21.

[22] Chaouat A, Bugnet A-S, Kadaoui N, Schott R, Enache I, Ducoloné A, et al. Severe Pulmonary Hypertension and Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine*. 2005 Jul 15;172(2):189–94

[23] Corson N, Armato SG, Labby ZE, Straus C, Starkey A, Gomberg-Maitland M. CT-Based Pulmonary Artery Measurements for the Assessment of Pulmonary Hypertension. *Academic Radiology*. 2014 Apr;21(4):523–30.

[24] Y. Matsuura, N. Kawata, N. Yanagawa, T. Sugiura, Y. Sakurai, M. Sato, K. Iesato, J. Terada, S. Sakao, Y. Tada, N. Tanabe, Y. Suzuki, K. Tatsumi, Quantitative assessment of cross-sectional area of small pulmonary vessels in patients with COPD using inspiratory and expiratory MDCT, *Eur J Radiol* 82(10) (2013) 1804-10.

- [25] K. Yoshimura, Y. Suzuki, T. Uto, J. Sato, S. Imokawa, T. Suda, Morphological changes in small pulmonary vessels are associated with severe acute exacerbation in chronic obstructive pulmonary disease, *Int J Chron Obstruct Pulmon Dis* 11 (2016) 1435-45.
- [26] Naeije R, Barberà JA. Pulmonary hypertension associated with COPD. *2001*;5(6):4
- [27] Kirkham PA, Barnes PJ. Oxidative Stress in COPD. *Chest*. 2013 Jul;144(1):266–73.
- [28] Haverkate E, Thompson SG, Pyke SD, Gallimore JR, Group MBP. Production of C-reactive protein and risk of coronary events in stable and unstable angina. *The Lancet*. Feb 1997;349(9050):462 6.
- [29] Thunström E, Glantz H, Fu M, Yucel-Lindberg T, Petzold M, Lindberg K, et al. Increased Inflammatory Activity in Nonobese Patients with Coronary Artery Disease and Obstructive Sleep Apnea. *Sleep*. march 2015;38(3):463 71.
- [30] Lyras L, Cairns NJ, Jenner A, Jenner P, Halliwell B. An Assessment of Oxidative Damage to Proteins, Lipids, and DNA in Brain from Patients with Alzheimer's Disease. *Journal of Neurochemistry*. 2002 Nov 18;68(5):2061–9.
- [31] Aguirre T, Matthijs G, Robberecht W, Tilkin P, Cassiman J-J. Mutational analysis of the Cu/Zn superoxide dismutase gene in 23 familial and 69 sporadic cases of amyotrophic lateral sclerosis in Belgium. *European Journal of Human Genetics*. 1999 Jul;7(5):599–602.
- [32] Shin S-K, Cho H-W, Song S-E, Song D-K. Catalase and nonalcoholic fatty liver disease. *Pflügers Archiv - European Journal of Physiology* [Internet]. 2018 Aug 17 [cited 2018 Aug 24]; Available from: <http://link.springer.com/10.1007/s00424-018-2195-z>
- [33] Almeida-Suhett CP, Graham A, Chen Y, Deuster P. Behavioral changes in male mice fed a high-fat diet are associated with IL-1 β expression in specific brain regions. *Physiology & Behavior*. 2017 Feb;169:130–40.
- [34] Woraruthai T, Charoenlap C, Hongsaprabhas C, Mutirangura A, Honsawek S. Alu hypermethylation and high oxidative stress in patients with musculoskeletal tumors. *PeerJ*. 2018 Aug 16;6:e5492.

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TITRE :

**MESURE QUANTITATIVE DU VOLUME VASCULAIRE PULMONAIRE TOTAL PAR
TOMODENSITOMETRIE CHEZ LES PATIENTS BPCO
CORRELATION AVEC LES EVENEMENTS CLINIQUES ET DONNEES BIOLOGIQUES**

CONCLUSION :

Une raréfaction de la vascularisation pulmonaire distale et des modifications des vaisseaux proximaux ont été démontrés dans la littérature chez les patients BPCO.

Nous avons étudié dans ce travail la corrélation entre différents paramètres TDM quantitatifs rendant compte de la vascularisation thoracique (volume vasculaire pulmonaire total (VVPT), VVPT normalisé (VVPTn), nombre total de vaisseaux (NTV), nombre de vaisseaux < 5 mm² (NTV5)) et la survenue d'évènements cliniques. Afin d'explorer la physiopathologie de cette relation, nous avons également étudié la corrélation de ces paramètres vasculaires aux données biologiques de l'inflammation et du stress oxydatif.

Ces paramètres vasculaires ont été obtenus par post-traitement de scanners thoraciques de routine sans injection par un logiciel développé localement. Notre cohorte était composée de 62 patients BPCO, dont la répartition était GOLD I n=8 (12,9%), GOLD II n=39 (62,9%), GOLD III n=10 (16,1%) et GOLD IV n=5 (8,1%). Les données cliniques d'hospitalisations, d'exacerbations, de consultations aux urgences et d'hospitalisation en réanimation ont été relevées jusqu'à 5 ans après le scanner. Les biomarqueurs de l'inflammation ainsi que les données EFR et du test de marche à 6 minutes ont été recueillies.

Concernant les facteurs pronostics, un VVPTn élevé constituait un facteur de risque significatif d'infection pulmonaire (OR=1.06 [1.01;1.12], p=0.02) et d'hospitalisation (OR=1.06 [1.01;1.12], p=0.01). Les variables NTV et NTV5 n'ont pas montré d'association significative avec les facteurs pronostics (p>0.05). Concernant les facteurs explicatifs physiopathologiques, un VVPTn élevé était significativement corrélé avec l'inflammation et en particulier à la CRP ultrasensible ($\beta= 3.12$ (0.84), p=0.001), et inversement corrélé avec le pouvoir total anti-oxydant du sérum ($\beta=-90.21$ (41.38), p=0.03) ainsi que la saturation en oxygène au repos ($\beta=-9.44$ (3.46) p=0.01).

Les résultats de notre étude pourraient suggérer chez les patients BPCO une atteinte du lit microvasculaire pulmonaire via des phénomènes inflammatoires chroniques et/ou une hypoxie chronique s'accompagnant d'un retentissement sur les gros vaisseaux d'amont, responsables à terme d'une dégradation du pronostic des patients.

VU ET PERMIS D'IMPRIMER

Grenoble, le : 12/09/2018

LE DOYEN



Pr. Patrice MORAND

LE PRÉSIDENT DE LA THÈSE



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