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REVIEW

Assessing pulmonary hypertension in COPD. Is there a role for computed tomography?

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Abstract: Pulmonary hypertension (PH) is a common complication of chronic obstructive pulmonary disease (COPD) and is associated with increased morbidity and mortality. Reference standard method to diagnose PH is right heart catheterization. Several non-invasive imaging techniques have been employed in the detection of PH. Among them, computed tomography (CT) is the most commonly used for phenotyping and detecting complications of COPD. Several CT findings have also been described in patients with severe PH. Nevertheless, CT analysis is currently based on visual findings which can lead to reproducibility failure. Therefore, there is a need for quantification in order to assess objective criteria. In this review, progresses in automated analyses of CT parameters and their values in predicting PH and COPD outcomes are presented.

Keywords: computed tomography, pulmonary hypertension, COPD, prediction

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms (ie, dyspnea, cough and/or sputum production) and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.[1] COPD has an increasing prevalence worldwide and is mainly caused by tobacco smoke exposure. Diagnosis is based on spirometry with a post-bronchodilator FEV_1/FVC ratio lower than 0.70.[2] The level of COPD severity is now assessed using both functional (ie, FEV_1 in percentage of predicted values) and clinical data (ie, symptoms scores (CAT and/or mMRC) and the number of exacerbations within the previous 12 months).[2]

COPD is frequently associated with comorbidities. Among them, pulmonary hypertension (PH) is causally related to COPD. PH is defined by a mean pulmonary arterial pressure (mPAP) equal or higher than 25 mmHg at rest, measured using the reference method right heart catheterization (RHC).[3–6] The prevalence of PH and the underlying pathophysiologic processes in patients suffering from COPD remain unclear. Indeed, prevalence increases with COPD severity, and its rate has been reported varying from 20% to 90%.[7–11] An increase of mPAP is associated with an increased number of hospitalizations, morbidity and mortality in COPD.[12–15] The few patients with severe PH secondary to COPD, defined at RHC as a mPAP ≥35 mmHg or mPAP ≥25 with cardiac index (CI) <2 l/min/m^2, are considered as a subgroup with potentially serious and high complication rate.[5] So far, only a few studies have evaluated the effects of vasodilator in patients with severe PH

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secondary to COPD, meaning that this subpopulation might benefit from a specific care.[16–18]

There are no specific clinical symptoms of PH, and this complication starts insidiously, the most common symptom being dyspnea.[8] PH in COPD patients has been shown to be associated with an increased exacerbation rate,[8] worsen exercise capacity[8] and a poorer prognosis.[8,13,15] For instance in a study from Andersen et al,[19] the survival rate was 63% for COPD patients without PH vs 37% in those with PH. The most reliable index of PH is the mPAP, a parameter so far measured only by RHC, an invasive technique which remains the reference method for the diagnosis of PH.[3,4] This unique test enables a direct assessment of various pulmonary arterial pressure indices, systolic, diastolic, mean and capillary pressures, as well as resistance, cardiac output and therefore enables to differentiate pre- and post-capillary PH,[20,21] a major way for assessing PH etiology. However, RHC can be responsible for the occurrence of adverse events, related to complication to venous access (such as hematoma, pneumothorax), but also those due to arrhythmias, hypotensive episodes due to vagal reaction or pulmonary vasoreactivity testing. Whereas RHC serious adverse events remain rare in experienced centers (ie, 1.1% and mortality is extremely rare),[22] RHC is not totally safe, especially in unstable patients. Thus, noninvasive diagnosis techniques able to reduce the delay in diagnosing PH and to avoid side effects of RHC are suitable. Echocardiography has been proposed to evaluate systolic pulmonary arterial pressure (sPAP), which is correlated with mPAP, but its specificity is low.[23] However, echocardiography remains the primary tool for patients screening, especially in others PH's etiologies.[4] Nevertheless, echocardiography may be technically difficult to perform, especially in patients with an inflated thorax and/or emphysema. Computed tomography (CT) is a common tool to investigate COPD and its role is crucial in the diagnosis and characterization of emphysema, airway disease, and advocated in various clinical situations such as follow-up, exacerbations, pre-operative surgery and lung transplantation.[2,24–27] CT is a useful tool to assess in vivo observation; nevertheless, radiation exposure risk is not null;[28] in addition, large inappropriate indications of this examination might lead to overrun radiology departments. Moreover, iodine contrast injection and repetitive CT acquisitions are needed to assess hemodynamic alterations related to PH which could increase risk of radiation and adverse reactions to contrast injection. Other interesting technics could be used to study PH, such as Dual energy CT,[29] or magnetic resonance imaging (MRI). MRI is much less employed in lung diseases due to the low signal intensity of the lung but recent improvements have been published[30–34] and MRI is currently the best tool for evaluating heart morphology and function,[35] or estimating pulmonary arterial pressure using phase contrast MRI.[36]

CT is currently performed for screening PH etiology, notably in the assessment of chronic thromboembolic PH, lung disease, pulmonary arterial hypertension and pulmonary veno-occlusive disease.[37–40] CT is also used as a prognostic marker in patients with PH.[41]

This review is focused on the role of CT in detecting PH in COPD patients. We will first describe the technical characteristics of CT and then we will discuss the morphological assessment of the parenchymal, bronchial and vascular compartments in COPD and their relationships with PH with a special interest in quantitative characterization.

COPD a multi-compartment disease

COPD is defined by functional irreversible airflow limitation but characteristic morphological changes are present in lung parenchyma, airways and pulmonary vasculature.[1,42] Airflow limitation can be, at least partially, explained by parenchymal destruction due to emphysema.[1] Emphysema is defined histologically by alveolar wall destruction and can be assessed visually using CT.[43–45] The severity of emphysema can also be measured by quantitative CT indices reflecting the low attenuation area due to lung destruction. These quantitative indices have been shown to correlate with macroscopic and microscopic changes histologically.[46,47]

Proximal bronchial wall thickening is a common feature in COPD.[48,49] Histological characteristics of proximal airways include increased infiltration of CD8(+) T lymphocytes, CD3+ T lymphocytes, macrophages.[48–50] This thickening appeared to be more important in a particular COPD-phenotype characterized by less severe respiratory disease, older subjects and higher rates of obesity and cardiovascular comorbidities.[51] Such a proximal thickening can be directly assessed by CT using 2D[52,53] and 3D reconstruction.[54–60]

Bronchial wall thickening is however predominant in distal airways.[61–65] At histological level, it associates luminal exudates, inflammatory cell infiltration and airway remodeling including peribronchial fibrosis, epithelial

metaplasia, mucous gland hypertrophy and increased bronchial smooth muscle mass of the small airways.[62,66] The higher the severity of COPD based on decreased FEV_1, the higher the histological abnormalities.[66] Moreover, inflammatory cell infiltration is related with tobacco smoking.[67] A loss of small airways has been observed using microCT, a high-resolution imaging technique dedicated to small samples or animal models, contributing to airflow limitation.[62] In humans, the small airway disease can be assessed two-folds morphologically: directly by showing centrilobular opacities and indirectly by using air trapping.[67–69] Such an air trapping has been shown to correlate with the number of inflammatory cells (*ie*, neutrophils and mast cells) infiltrating the bronchial smooth muscle layer.[67]

It has been shown that the toxicity of tobacco smoke affects bronchi and parenchyma, but can also directly alter pulmonary vessels both in animals[70] and humans.[6,71] At histological level, pulmonary arterial remodeling appeared to be more important in COPD than in control subjects, and is particularly important in upper lobe and in small muscular pulmonary arteries.[72] Those vessel alterations are multiples and can happen at initial stage of COPD[71] with endothelial dysfunction, inflammation, suggesting that the history of PH in COPD might be related with cigarette-smoke-induced endothelial alterations.[73,74] The quantitative amount of emphysema in COPD was often negatively correlated to pulmonary microvasculature abnormalities measured using CT,[75–79] except for Wrobel et al,[72] which did not find any significant correlation.

CT technical considerations

CT scan is the most reliable imaging modality for imaging pulmonary diseases, and it is available and commonly used in routine practice. The new generation of multidetector CT scanners allows acquisition of the whole lung in one breath hold with a submillimetric slice thickness and isotropic voxels using adequate matrix.

The COPD Gene study provides recommendations to standardize CT acquisition parameters in order to obtain high signal-to-noise ratio and accordingly accurate assessment of the images.[80] Thin sections with non-contrast-enhanced volumetric acquisition is a standard technique for COPD imaging.[81] However, intravenous iodinated contrast material is necessary in case of exacerbations or suspected pulmonary embolism. Standard reconstruction algorithm (smooth filter) is required for quantitative automatic analysis.[82] Spirometric gated acquisition have been proposed to improve quantitative assessment, but is only used in dedicated research programs due to its complexity and low availability.[83] Although COPD patients are older and radiation risks are thus minimized, balance between radiation dose and image quality should be considered. Misevaluation of quantitative parameters because of noisy images leads to standard tube parameters (kVp and mAs).[84] However, low-dose CT acquisition with new iterative reconstruction algorithms allows noise reduction with acceptable quantitative measurements.[83,85]

Lung parenchyma

Historically, parenchymal alteration, and more precisely, emphysema, has been the first lung component investigated in order to explain PH in COPD. Indeed, emphysema is a major characteristic of COPD that could be quantified in patients when CT is performed. At CT, emphysema can be quantitatively evaluated, using low attenuation area percent (LAA%) derived from the voxel frequency distribution histogram. Several thresholds have been proposed but the most commonly employed is the value of –950 Hounsfield units (HU)[45,46,86–89] (see Figure 1). It has been initially hypothesized that emphysema was correlated with mPAP. However, surprisingly, no relationship between PH and emphysema has been demonstrated neither in human nor in animal models.[7,44,45,90,91] In addition, no significant difference in LAA% between COPD patients with or without PH was observed.[45,92,93] Nonetheless, one single study observed that among COPD patients with PH, the LAA% measured using automated CT was correlated with right ventricular (RV) dysfunction.[94] Emphysema can also be reflected using CT scan with the threshold of −960 HU, the evaluation of the first percentile,[95] or in longitudinal studies, the 15th percentile is preferred to follow-up emphysema changes.[96]

Proximal bronchi

Bronchi can be studied using CT with 2D[52,53] or 3D[54–60] acquisitions. Various methods of bronchial segmentation and various parameters have been proposed, with so far no consensus (see Figure 2). Lumen area, wall area, wall area %, wall thickness and -Pi10, that reflects the normalized wall area of a theoretical 10-mm bronchi section area, have been proposed as indices for quantitating the severity of bronchial wall changes.[45,52,86,89,97–101] We have demonstrated that bronchial thickness assessed by CT was increased in COPD patients with PH as compared to that of COPD patients without PH, whereas demographic, clinical and functional data (except PaO_2 and 6 mins walk test

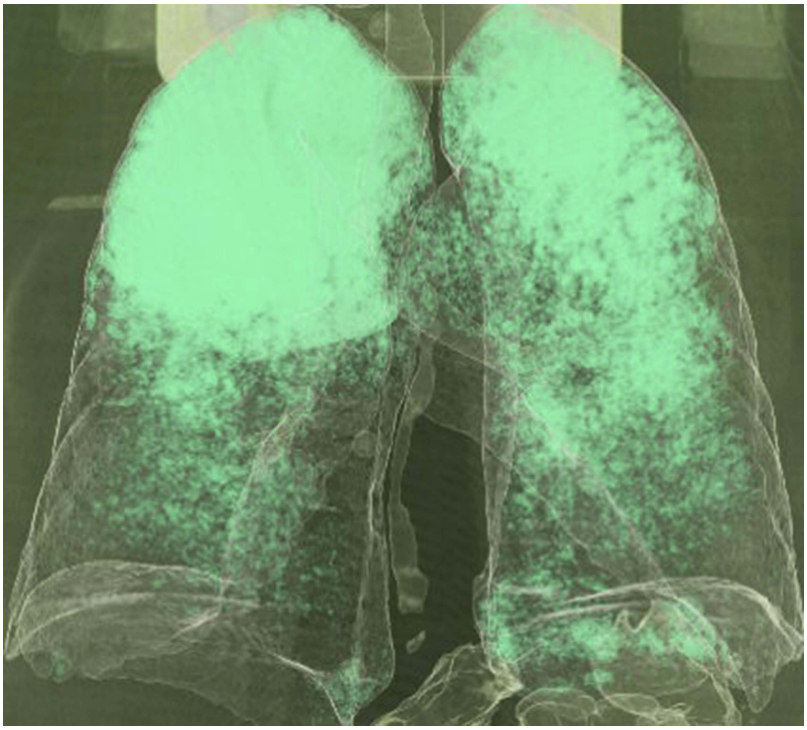

Figure 1 Reconstructed chest CT scan in COPD patient. This image was acquired with high-spatial-frequency algorithm reconstruction using fully automated Pulmo3D software (Siemens, Munich, Germany). Low attenuation area (LAA%) was derived from the voxel frequency distribution histogram and represented the percentage of lung voxels less than −950 HU. In this COPD patient, LAA value was 23%.
Abbreviations: COPD, chronic obstructive pulmonary disease; CT, computed tomography.

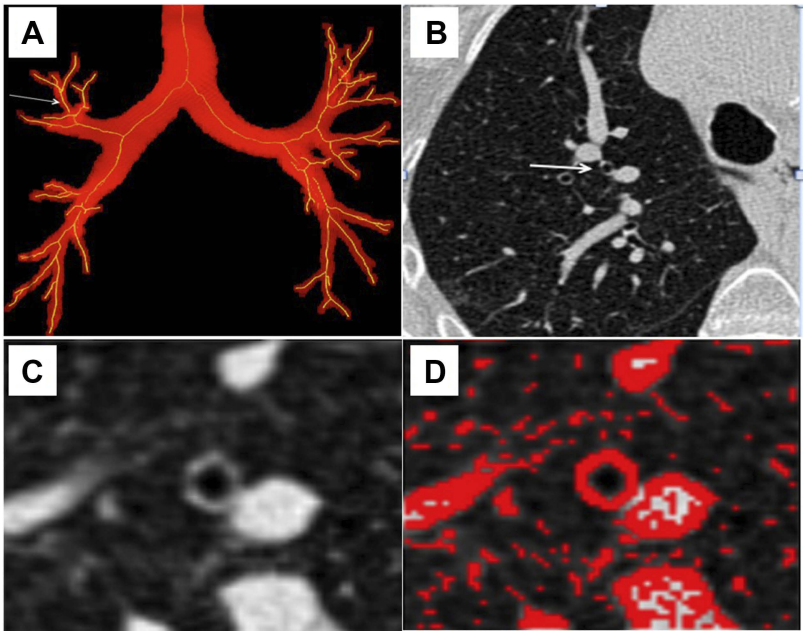

Figure 2 Bronchi segmentation. (**A**) Frontal view of a propagation algorithm to obtain a skeleton binary volume based on bi-thresholding. Arrow shows bronchi in which measurements were assessed. (**B**) Peripheral bronchus is designated (arrow) on a native transverse thin-section CT. (**C**) Thin-section CT scan used to obtain measurements. (**D**) A Laplacian of Gaussian algorithm was assessed to segment the designed airway and measure bronchial thickness.
Abbreviation: CT, computed tomography.

distance, not surprisingly) remain unchanged.[45] Moreover, a correlation between bronchial wall thickness and mPAP has been reported both in PH[45] and in severe PH secondary to COPD.[86,102] In addition, bronchial wall thickness measured using CT was correlated to histological measurements of airway remodeling,[52] to exacerbation frequency,[103] respiratory symptoms[89] and to FEV1%.[104]

Small airways

Since obstruction of small airways, defined as airways with a diameter under 2 mm, has been shown to be the main determinant of obstruction in COPD,[62–65] some imaging technics have intended to characterize small airway disease in COPD. Mosaic attenuation at inspiratory and air trapping at expiratory CT reflect small airway disease. Both are related to a decreased lung attenuation and therefore cannot be easily distinguished from emphysema.[105] However, we have found that air trapping was correlated with inflammatory cell infiltration and might reflect peripheral airway obstruction in patients exposed to cigarette smoking.[67] Galbán et al have assessed both expiratory and inspiratory CT using parametric response map in order to estimate functional small airway disease in COPD patients.[106] Parametric response map was able to differentiate COPD phenotypes. In addition, Matsuoka et al calculated relative volume change (expiratory minus inspiratory relative volume) using CT with the threshold of −860 HU that was correlated with airway dysfunction (ie, assessed at PFTs) in COPD regardless of the degree of emphysema.[68] To the best of our knowledge, there is no study dedicated to the small airways of COPD patients with PH using CT.

Central vessels

In COPD, a correlation has been shown between mPAP and enlargement of the main pulmonary artery truncus (MAP) diameter, and this increase is observed when MAP is normalized by ascending aorta diameter (MAP/AO).[86,107–110] Usually, normalization is made on ascending aorta[107,108,111,112] (see Figure 3) but it has also been done on descending aorta.[21] Usually, MAP widest dimension is measured on axial CT images, on inspiratory acquisition, at bifurcation level, and, AO is measured on the same image.[107,108,111,112] Descending aorta is also measured at the same level.[112] Thresholds values to detect PH in COPD patients are: MAP ≥29 mm[21,113,114] and MAP/AO>1.[107,110,111,115,116]

Increased MAP/AO ratio, a very simple index measured on a routine CT acquisition, has been shown linked to an increased risk of exacerbation in COPD[108,111,117] and a lower 6-mins walk distance.[118] Mortality in COPD population was also correlated to MAP/AO ratio in some reports[115,119] but not in others.[108,110] Interestingly, this ratio was not correlated to mortality in the general population.[119] However, in healthy children, the ratio MAP/AO is higher than one, so the threshold of 1 cannot be applied in children.[112]

Pulmonary artery distensibility, that reflects elasticity using volume variations of the MAP between diastole and systole, is decreased in PH.[3,4,120] The increase of stiffness is

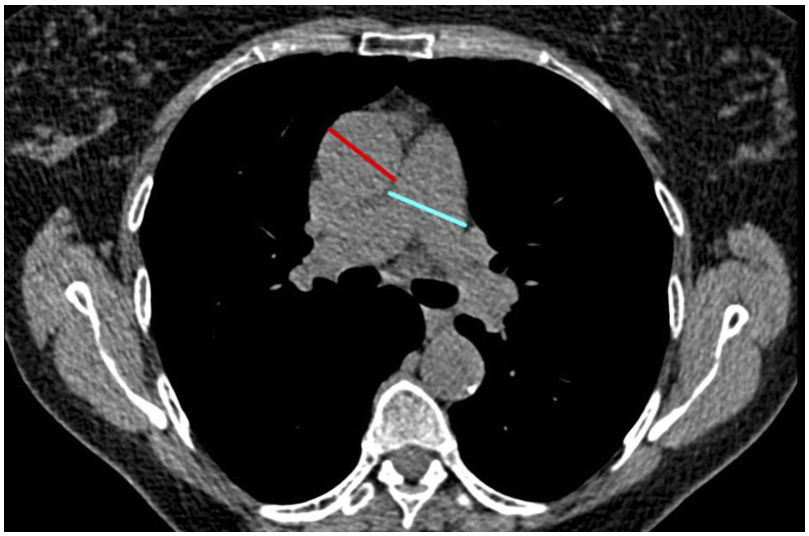

Figure 3 Pulmonary artery and aorta measurements. Ratio measurement obtained in a COPD patient in a transverse CT section.
Abbreviations: COPD, chronic obstructive pulmonary disease; CT, computed tomography.

also observed in group 3 of PH[121] and in PH related to COPD.[122] Cardiac magnetic resonance (CMR) or ECG-gated CT can be also used to evaluate PA stiffness.[3,4,120,121]

In addition, dynamic-contrast-enhanced CT can be used to discriminate patients with or without PH from different etiology.[123] A delayed flow of contrast and a reduced bolus propagation speed were observed in PH in comparison to control patients. Regions of interests were placed in the MAP and in the left and right pulmonary arteries. However, this study presented some limitations since bolus propagation also reflects the left heart function, the respiratory function and the speed of injection.[123]

Small vessels

The segmental pulmonary artery-to-bronchus ratio, semi-quantitatively evaluated for apical and posterior segments that run perpendicularly to the axial CT-scan, is positively correlated with mPAP.[124] Ratio>1 in three or more lobes is specific of the presence of PH[113,124] in group 3 of PH classification that also comprise COPD.[125] In the same way, the size of the segmental arterial diameters is also positively correlated with mPAP[124] in group 3 of PH.[125]

Regarding small pulmonary arteries, several of their characteristics have been studied, notably, number, volumes and areas. CT is an efficient tool in order to evaluate in vivo alterations of vessels, follow-up of illness or evaluating drug effects.

Some tools have been developed using 2D[35,79,86,102] (see Figure 4) or 3D[78,118,126] reconstructions.

Using 2D reconstruction on CT images, an automated measurement has been assessed using a free software Image J. These automated measurements allowed the visualization of small vessels alterations first on 3 CT slices[44,127,128] and then on the whole lung.[86,102] Software enables calculation of the percentage of cross-sectional areas (CSA%) of small pulmonary vessels under 5 mm^2 ($\%CSA_{<5}$) and between 5 and 10 mm^2 (CSA_{5-10}), normalized by lung area, measuring subsubsegmental and subsegmental levels, respectively. Thus, in COPD patients without severe PH, the correlation between $\%CSA_{<5}$ and mPAP was negative[44,86] whereas in COPD with severe PH correlation was positive.[86,102]

The 3D reconstruction technique allowed to measure volumes of small vessels.[78,118,129] In both studies,[78,118] index using 3D for assessment of pulmonary vessels was negatively correlated with MAP. For Ma et al,[78] 3D and 2D techniques were correlated. Studies using 2D and 3D are in the same line and showed a negative correlation between small pulmonary vessels and mPAP in COPD patients with most of the time moderate PH. As mentioned by others, all those vascular impairments support a vascular etiology of smoking-induced lung disease.[6,130] CT metrics, such as $\%CSA_{<5}$, also allowed evaluation of the effect of pulmonary vasodilators in patients with PH related to COPD.[79]

In the automated measurements previously reported, pulmonary arteries were never separated from veins and this may affect the sensitivity of the technique. Tools have been developed in 3D in order to circumvent this limitation but not employed, to the best of our knowledge, for evaluating PH in COPD patients.[126,129,131,132] A summary of vessels analyses is presented in Table 1.

Scores

As mentioned above, several parameters reflecting various components in COPD are modified in COPD patients with PH. Building a score involving these parameters can be a strategy to improve the detection and the severity assessment of PH in COPD.

Tan et al have associated MAP ≥29 mm with artery-to-bronchus ratio >1 in 3 or 4 lobes and have reached a specificity of 100% for detecting PH in patients suffering from parenchymal lung diseases.[113]

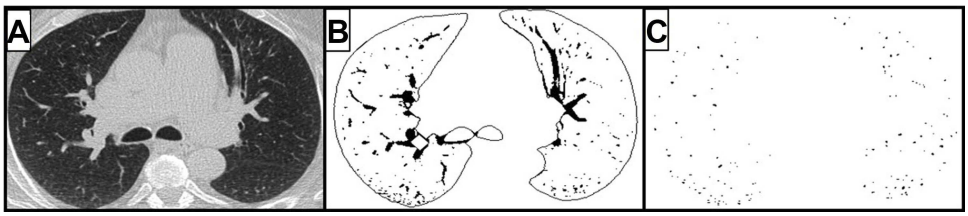

Figure 4 Measurement of cross-sectional areas (CSA) of small pulmonary vessels using Image J free-software. (**A**) CT image segmented within the threshold values from −500 to −1024 HU of lung field. (**B**) Segmented image segmented into binary images. (**C**) Mask image for the particle analysis after setting circularity within [0.9–1.0] and vessel size within [0–5] mm^2.
Abbreviation: CT, computed tomography.

Table 1 Summary of vessels analyzes in COPD with PH

Publication year	First author	Journal	CT findings	Qualitative /quantitative /Automated /manual	No. of patients	Screened population	Search for
2014	Iyer et al[107]	Chest	MAP/AO>1 better than echocardiography to evaluate PH in COPD patients	Quantitative manual	60	Severe COPD	mPAP ≥ 25 mmHg
2017	Iliaz S et al[108]	Clin Respir J	MAP/AO correlated with PH, number of exacerbation, not with mortality	Quantitative manual	156	COPD exacerbation	Number of COPD exacerbation 1 year after the first one
2017	Cuttica MJ et al[109]	Int J Chron Obstruct Pulmon Dis	MAP/AO associated with pulmonary hemodynamics and right heart structure and function changes	Semi-quantitative manual	88	Mil-to-moderately severe COPD	mPAP ≥ 25 mmHg
2016	Ortaç Ersoy E et al[110]	J Crit Care	MAP/AO≥1 associated with pulmonary hypertension, but not with mortality	Quantitative manual	106	COPD	mPAP ≥ 25 mmHg
2016	Coste F et al[86]	Thorax	% cross-sectional area of small pulmonary vessels <5 mm^2 ($\%CSA_{<5}$) is negatively correlated to mPAP for moderated PH (25–35 mmHg), and positively correlated to mPAP for severe PH (>35 mmHg)	Quantitative automated	105	COPD	mPAP ≥ 25 mmHg 35 mmHg
2012	Wells JM et al[111]	NEJM	MAP/AO>1 associated with severe COPD exacerbation	Quantitative manual	3464	Smokers with COPD	COPD exacerbation
2015	Compton GL et al[112]	AJR	Description of technical measurements of MAP/AO in children, threshold is greater than 1, closer to 1.09	Quantitative manual	400	General children population	Threshold of MAP/AO in children
2011	Chan AL et al[21]	BMC Med Imaging	Significant predictors of PH: MAP≥ 29 mm, MAP/AO≥ 0.84, MAP/descending aorta≥ 1.29 mm	Quantitative manual	101	Heterogenous diagnoses	mPAP ≥ 25 mmHg
1998	Tan RT et al[113]	Chest	MAP≥ 29 mm. Artery to bronchus ratio ≥1 in 3 or 4 lobes	Quantitative manual	28	Parenchymal lung disease	mPAP ≥ 20 mmHg
2012	Truong QA et al[114]	Circ Cardiovasc Imaging	MAP≥ 29 mm in men, MAP≥ 27 mm in women, MAP/AO≥ 0.9	Quantitative manual	3171	Asymptomatic community-based population	90^{th} percentile
2014	Shin S et al[115]	Repir Med	MAP/AO>1 associated with PH in patients with COPD, independent predictor of mortality	Quantitative manual	65	Advanced COPD	mPAP ≥ 25 mmHg survival

(*Continued*)

Table 1 (Continued).

Publication year	First author	Journal	CT findings	Qualitative /quantitative /Automated /manual	No. of patients	Screened population	Search for
2016	Mohamed Hoesein FA et al[116]	Lung	MAP≥ 30 mm and MAP/AO> 1 associated with PH	Quantitative manual	92	COPD	mPAP ≥ 25 mmHg
2016	Wells JM et al[117]	Chest	MAP/AO>1 predict exacerbation of COPD	Quantitative manual	134	Patient with acute exacerbation of COPD	Predict clinical outcome with MAP/AO
2015	Wells JM et al[118]	Circ Cardiovasc Imaging	Intraparenchymal pulmonary blood vessel volume and the volume of distal vessels with cross-sectional area (CSA) of <5 mm^2 negatively correlated with MAP/AO. MAP/AO, MAP negatively correlated with 6MWT	Quantitative automated	24	Non severe COPD	MAP/AO>1
2017	Terzikhan N et al[119]	Eur Respir J	In general population, MAP/AO >1 not associated with mortality. In COPD population, MAP/AO >1 associated with mortality	Quantitative manual	2197	General and COPD populations	Pronostic information of MAP/AO
2009	Revel MP et al[120]	Radiology	Decreased pulmonary arterial distensibility in PH, ECG-gated CT	Quantitative manual	45	Different group 1, 2 etiology of PH	mPAP ≥ 25 mmHg
2014	Pienn M et al[123]	Eur Radiol	Reduced bolus propagation speed and time differences between contrast material peaks in PH patients, using dynamic-contrast-enhanced CT	Quantitative semi-automated	33	Different potential etiology of PH, notably lung disease, and control patients	mPAP ≥ 25 mmHg
2010	Devaraj A et al[124]	Radiology	MAP/AO and Artery to bronchus ratio correlated with mPAP Size of segmental arterial diameter correlated positively with mPAP	Quantitative manual	77	Spectrum of disease associated with PH (Groups 1, 3, 4,5)	mPAP ≥ 25 mmHg 34 mmHg
2010	Matsuoka S et al[44]	Am J Respir Crit Care Med	% cross-sectional area of small pulmonary vessels <5 mm^2 ($\%CSA_{<5}$) is negatively correlated to mPAP for moderated PH, in severe emphysema population	Quantitative automated	79	COPD	Correlation with mPAP
2015	Ando K et al[79]	Lung	$\%CSA_{<5}$ used to assess pulmonary vasodilators longitudinal evaluation	Quantitative automated	42	COPD	Effect of pulmonary vasodilators in COPD-PH patients

(*Continued*)

Table 1 (Continued).

Publication year	First author	Journal	CT findings	Qualitative /quantitative /Automated /manual	No. of patients	Screened population	Search for
2017	Ma J et al[78]	J Xray Sci Technol	3D tool able to detect the mean lumen area that was negatively correlated with MAP, and mean number of vessels negatively correlated with emphysema (LAA%, −950 HU)	Quantitative automated	102	Heavy smokers	Computerized scheme to detect pulmonary vessels
2011	Matsuoka S et al[76]	Acad. Radiol.	Negative correlation between $\%CSA_{<5}$ and LAA%	Quantitative automated	191	Smoking history	Evaluate correlation small vessels-emphysema
2011	Uejima I et al[128]	Jpn J Radiol	Positive correlation between $\%CSA_{<5}$ and FEV_1/FVC	Quantitative automated	30	Non smokers	Evaluate correlation small vessels- PFTs
2013	Park S et al[129]	Med Phys	Assessing volumetric technic allowing pulmonary artery/vein separation	Quantitative automated	10	COPD	Evaluate volumetric technic allowing pulmonary artery/vein separation
2016	Iyer S et al[130]	Am J Respir Crit Care Med	After sildenafil arterial CSA and perfused blood volume decreased only in centriacinar emphysema patients, using dual-energy CT perfused blood volume	Quantitative automated	17	Current smokers	Effect of sildenafil on vascular perfusion
2016	Payer C et al[131]	Med Image Anal	Assessing 3D technic allowing pulmonary artery/vein separation	Quantitative automated	25	Lung vascular disease	Evaluate 3D technic allowing pulmonary artery/vein separation
2016	Charbonnier JP et al[132]	IEEE Trans Med Imaging	Automatic separation and classification of pulmonary arteries and veins using CT with an accuracy of 0.89	Quantitative automated	55	Lung cancer	Evaluate separation and classification of pulmonary arteries/veins
2019	Coste F et al[102]	Int J Chron Obstruct Pulmon Dis	% cross-sectional area of small pulmonary vessels <5 mm^2 ($\%CSA_{<5}$) is positively correlated to mPAP for severe PH (>35 mmHg)	Quantitative automated	24	COPD	mPAP ≥35 mmHg

Abbreviations: COPD, chronic obstructive pulmonary disease; CT, computed tomography; PH, pulmonary hypertension.

Table 2 Summary of scores built in order to diagnose PH or severe PH in lung disease or COPD

Publication year	First author	Journal	Score	CT metrics	No. of patients	Screened population	Search for	Sens. Spe.	PPV NPV
1998	Tan RT et al[113]	Chest	MAP ≥29 mm + artery to bronchus ratio ≥1 in 3 or 4 lobes	MAP+A/B	28	Parenchymal lung disease	mPAP≥ 20 mmHg	NA 1.00	NA
2010	Devaraj A et al[124]	Radiology	MAP/AO + Right ventricular systolic pressure (echocardiography)	MAP/AO	77	Spectrum of disease associated with PH (Groups 1, 3, 4, 5)	mPAP≥ 25 mmHg 34 mmHg	 0.96 0.59 0.73 0.88	NA
2016	Coste F et al[86]	Thorax	"Paw score": %cross-sectional area of small pulmonary vessels <5 mm^2+ bronchial wall thickening + PaO_2	$\%CSA_{<5}$+ WT	105	COPD	mPAP≥ 35 mmHg	0.75 0.80	0.36 0.96
2019	Coste F et al[102]	Int J Chron Obstruct Pulmon Dis	"Paw score": %cross-sectional area of small pulmonary vessels <5 mm^2+ bronchial wall thickening + PaO_2	$\%CSA_{<5}$+ WT	24	COPD	mPAP≥ 35 mmHg	0.88 NA	NA NA
2018	Johns CS et al[133]	Eur. Radio.	"CMR-RV": RV mass + septal angle		102	COPD	mPAP≥ 25 mmHg	0.90 0.79	0.96 0.58
			"CMR-PA/RV": RV mass + septal angle + MAP measurement	MAP measurement				0.92 0.80	0.96 0.63
			"α-index": RV ejection fraction + minimal MAP size	Minimal MAP size				1.00 0.13	0.87 1.00

Abbreviations: COPD, chronic obstructive pulmonary disease; CT, computed tomography; NA, not attributed; NPV, negative predictive value; PPV, predictive positive value; PH, pulmonary hypertension.

Another index was composed of MAP/AO and right ventricular systolic pressure (RVSP) derived from echocardiography and was correlated with mPAP (R^2=0.55)[124] for group 1, 3, 4 and 5 of PH.[3,4]

Johns et al mentioned many RV parameters manually measured that are correlated with PH evolution in COPD patients.[133] They tried to identify the best combination able to predict PH. First combination "cardiac magnetic resonance-RV" ("CMR-RV") included RV mass and septal angle,[134] second "CMR PA/RV" combined RV mass, septal angle and MAP measurements, and the third "α-index" encompass RV ejection fraction (RVEF) and minimal MAP size.[135] The second model was the best model able to predict mPAP ≥25 mmHg. The same team also confirmed the interest of those results in another recent study using a validation cohort.[136]

We have built a "paw score" in order to predict severe PH in COPD patients combining CT automated measurements of bronchial wall thickness and pulmonary small vessels areas (%$CSA_{<5}$) with PaO_2[86,102]

The various scores and their sensitivity are reported in Table 2.

Conclusion

PH secondary to COPD is a serious complication that is important to predict with non-invasive tools. Integration of imaging into standard clinical practice is an asset for patient's care. Automated measurements of markers reflecting pulmonary small vessels, bronchial wall and emphysema changes are emerging and might be used routinely in the future for predicting PH or severe PH. All these CT markers could be used in morpho-phenotyping studies. Further studies are required to assess their prognostic impact and follow-up under treatment.

Abbreviations

AO, aorta; COPD, chronic obstructive pulmonary disease; CMR, cardiac magnetic resonance; CT, computed tomography; FEV_1, forced expiratory volume in 1 second; FVC, forced volume capacity; HU, Hounsfield units; LAA%, low-attenuation area percentage; m, s, dPAP, mean, systolic, diastolic pulmonary arterial pressure; MAP, Main Pulmonary Artery truncus; MRI, magnetic resonance imaging; NA, not attributed; NPV, negative predictive value; PA, pulmonary artery; PaO_2, arterial partial pressure of oxygen (mmHg); PFT: pulmonary Function test; PH, pulmonary hypertension; PPV, positive predictive value; RHC, right heart catheterization; RV, right ventricle; WA, bronchial Wall Area (mm); WT, mean bronchial Wall Thickness (mm); 6MWT, 6 mins walk tests; %$CSA_{<5}$, percentage of total cross-sectional area of vessels less than 5 mm^2 normalized by lung area.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Professor Laurent reports personal fees from Boehringer-Ingelheim, Roche, and Chiesi, outside the submitted work. Professor Pierre-Olivier Girodet reports personal fees, non-financial support from Novartis, personal fees, non-financial support from Chiesi, personal fees, non-financial support from Boehringer-Ingelheim, personal fees, non-financial support from AstraZeneca, personal fees, non-financial support from ALK, outside the submitted work. Professor Patrick Berger reports grants from Novartis, personal fees, non-financial support from AstraZeneca, personal fees, non-financial support from Menarini, personal fees, non-financial support from Circassia, personal fees, non-financial support from Sanofi, personal fees from Teva, outside the submitted work; in addition, Prof Berger has a patent Geometric characterization of airways using MRI. 22605-FR pending. The authors report no other conflicts of interest in this work.

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