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ORIGINAL RESEARCH

Expiratory Venous Volume and Arterial Tortuosity are Associated with Disease Severity and Mortality Risk in Patients with COPD: Results from COSYCONET

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Purpose: The aim of this study was to evaluate the association between computed tomography (CT) quantitative pulmonary vessel morphology and lung function, disease severity, and mortality risk in patients with chronic obstructive pulmonary disease (COPD).

Patients and Methods: Participants of the prospective nationwide COSYCONET cohort study with paired inspiratory-expiratory CT were included. Fully automatic software, developed in-house, segmented arterial and venous pulmonary vessels and quantified volume and tortuosity on inspiratory and expiratory scans. The association between vessel volume normalised to lung volume and tortuosity versus lung function (forced expiratory volume in 1 sec [FEV_1]), air trapping (residual volume to total lung capacity ratio [RV/TLC]), transfer factor for carbon monoxide (TLCO), disease severity in terms of Global Initiative for Chronic Obstructive Lung Disease (GOLD) group D, and mortality were analysed by linear, logistic or Cox proportional hazard regression.

Results: Complete data were available from 138 patients (39% female, mean age 65 years). FEV_1, RV/TLC and TLCO, all as % predicted, were significantly ($p < 0.05$ each) associated with expiratory vessel characteristics, predominantly venous volume and arterial tortuosity. Associations with inspiratory vessel characteristics were absent or negligible. The patterns were similar for relationships between GOLD D and mortality with vessel characteristics. Expiratory venous volume was an independent predictor of mortality, in addition to FEV_1.

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Conclusion: By using automated software in patients with COPD, clinically relevant information on pulmonary vasculature can be extracted from expiratory CT scans (although not inspiratory scans); in particular, expiratory pulmonary venous volume predicted mortality.
Trial Registration: NCT01245933.
Keywords: COPD, computed tomography, pulmonary vasculature, vessel volume, vessel tortuosity, lung function

Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by alveolar destruction, peribronchial fibrosis, and bronchial and vascular remodelling.[1–3] In addition to pulmonary hypertension, which can occur as vascular alterations,[4] morphological and functional changes of the central and peripheral pulmonary vasculature are typically observed in patients with COPD. Furthermore, it has been proposed that the initial effects of smoking on the lung may be due to detrimental effects on pulmonary vasculature.[5–7]

In clinical practice, the process of phenotyping COPD is increasingly supported by conventional, non-contrast-enhanced chest computed tomography (CT) scans, mostly focusing on airway morphology and the presence of lung emphysema.[8] Alterations in pulmonary vasculature are less often considered, although these changes are known to be associated with increased exacerbation risk[9–12] and the decline in lung function over time.[13,14] One challenge when assessing the characteristics of pulmonary vasculature (eg length, tortuosity and volume) is that the appearance on CT scans depends on the ventilatory phase and lung volume.[15,16] Routine CT scans are commonly performed at full inspiration, as this is considered best suited for the evaluation of lung parenchyma; less information on the diagnostic value of expiratory CT scans is available, particularly with regard to the pulmonary vasculature. In a recent study, expiratory scans were superior to inspiratory scans in terms of the association between vessel volumes and COPD severity.[17,18] However, these analyses did not include other important clinical characteristics, such as exacerbations, symptoms, or mortality risk.

COSYCONET (COPD and SYstemic consequences-COmorbidities NETwork) is an ongoing, long-term, prospective observational multi-centre cohort of patients with COPD (ClinicalTrials.gov NCT01245933). Previous analyses utilising CT data from COSYCONET were limited to inspiratory scans and did not include parameters of vasculature.[19–23] However, data from both inspiratory and expiratory CT scans were collected, following protocols that were similar to those used in routine clinical practice, and without special equipment. The information used in the present study was extracted using fully automatic software tools developed in-house. Such tools can be used for the segmentation of parenchymal and vascular structures,[19,22–24] offering the potential for application to clinical practice with minimal additional effort. Therefore, we studied the potential utility of the automated assessment of intrapulmonary vessel characteristics in inspiratory and expiratory CT scans for phenotyping and risk evaluation of patients with COPD.

Materials and Methods

Study Design and Population

The study population was a subgroup of the German cohort study COSYCONET, which was initiated in 2010 in 31 study centres. Patients aged 40 years and older with a diagnosis of COPD were included. Details of the inclusion and exclusion criteria, study protocol and assessments have been published previously.[20,21] Patients had follow-up visits 6, 18 and 36 months after inclusion (visits 2–4).

Briefly, of the 1463 COSYCONET patients who completed visit 4, 602 patients underwent CT scans, 138 of whom had complete data at inspiration and expiration (see flow chart in Figure 1).

Inspiratory and expiratory CT scans[20,21,25] were captured in the same examination on a separate study day that was close to visit 4 (in a few cases visit 3); lung function and clinical data from the closest visit were used to characterise patients at the time of the CT scans. The study was performed in accordance with the Declaration of Helsinki and STROBE recommendations, after approval by the Ethics Committee of the University of Marburg (coordinating site), and all other study centres. CT scans were approved by the Ethics Committee of the University of Heidelberg (coordinating site for radiologic examinations) and the participating study centres. All patients provided written informed consent.

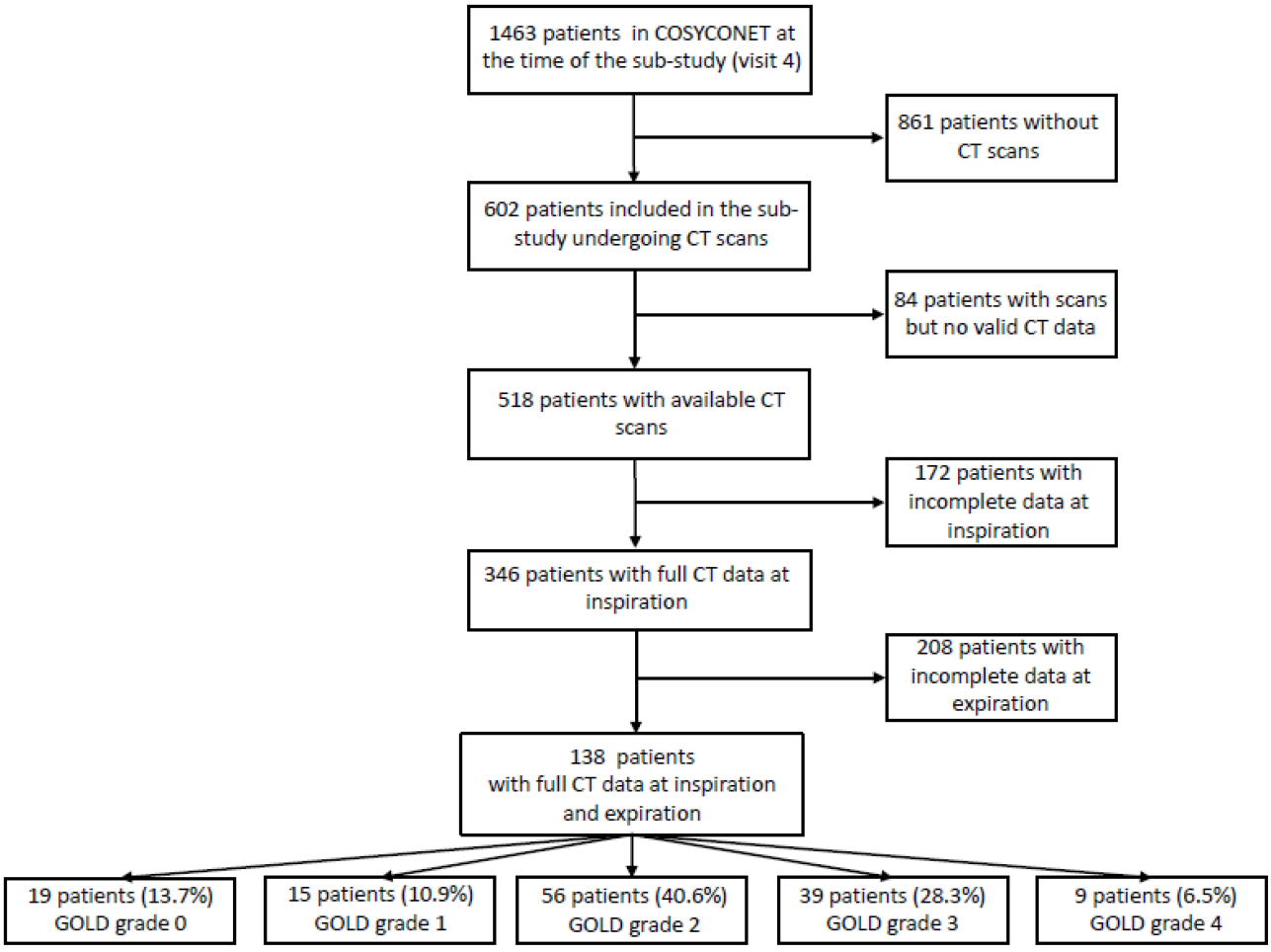

Figure 1 Flowchart illustrating the inclusion and exclusion criteria of patients at study entry. Of 1463 COSYCONET patients admitted for the visit 4, 602 patients undergoing CT scans were included in the present sub-study. Of 346 patients with full CT data at inspiration, 138 patients had complete data at inspiration and expiration. 13.7%, 10.9%, 40.6%, 28.3% and 6.5% of the included patients were categorised with GOLD grade 0–4, respectively.

Assessments

Clinical data included age, sex, body-mass index (BMI), smoking status, comorbidities, lung function, symptoms, and exacerbations.[21] From spirometry maneuvers, we determined forced expiratory volume in 1 sec (FEV_1) as a measure of airway obstruction and forced vital capacity (FVC); from body plethysmography we captured the ratio of residual volume to total lung capacity (RV/TLC) as a measure of air trapping, and the transfer factor for carbon monoxide (TLCO) as a measure of lung diffusion (gas uptake) capacity. These were expressed as % predicted, with predicted values for spirometry and TLCO taken from the Global Lung Function Initiative (GLI),[26,27] and those of body plethysmography from the European Coal and Steel Community (ECSC) values.[28] Based on the spirometry results, patients were categorised into Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades 1–4, if FEV_1/FVC was <0.7,[29] and otherwise as the former GOLD grade 0.[30–32]

Respiratory symptom burden was assessed via the modified Medical Research Council dyspnoea scale (mMRC),[33] which was used to categorise patients into GOLD groups A, B, C and D.[29,30,34] In particular, we compared GOLD group D, who had combined higher symptom burden and exacerbation risk, with the pooled group ABC, a comparison that had been found useful in previous COSYCONET analyses.[25] The occurrence of death was determined between visit 4 and visit 6 of COSYCONET (36 to 72 months after enrolment).[35]

Computed Tomography

Low-dose non-enhanced CT was performed with at least 40-row detector array scanners,[20,36] according to a standardised phantom-controlled protocol based on the recommendations of the thoracic imaging workshop of the German Radiological

Society.[37] The protocol included end-inspiratory and end-expiratory acquisitions of the entire lung, and was adapted to the local technical specifications of the scanners, if necessary.[21,38,39] Technical details can be found in the Supplementary Table 1.

CT scans were visualised using the OsiriX viewer (64-bit, Pixmeo SARL, Geneva, Switzerland), with their quality evaluated by two experienced thoracic radiologists (HUK, JB). The pulmonary vessels with diameters between 2 and 10 mm were segmented by fully automated software as previously reported.[40] This software first performed a vessel extraction from CT scans, followed by a differentiation into arterial and venous vessels and volumetric quantification. A more detailed description of the segmentation process is presented in the Supplementary Figure S1. Examples of the vessel segmentations in inspiration and expiration for a patient are shown in Figure 2. In addition to vessel volumes, data on tortuosity were obtained by calculating the

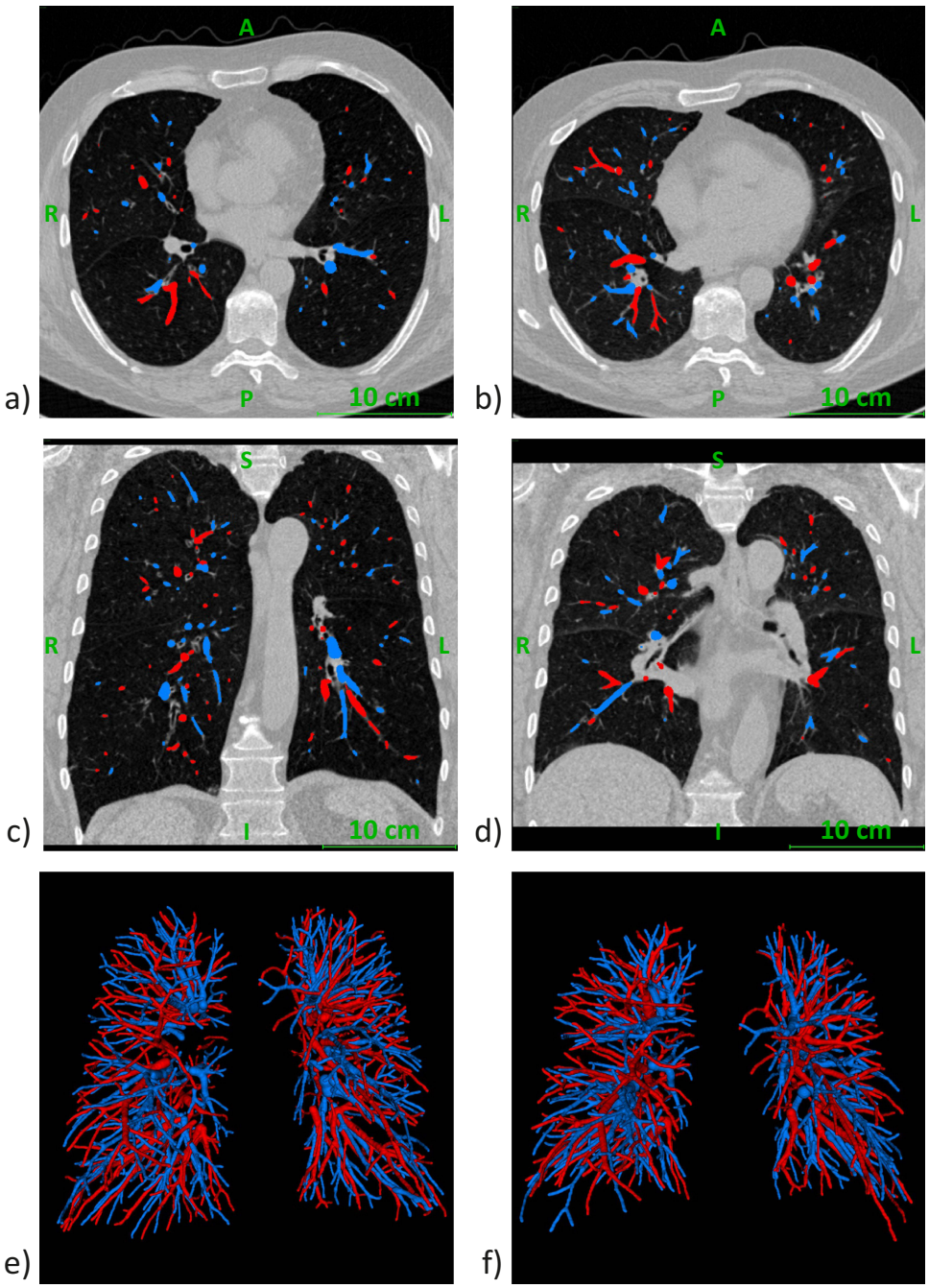

Figure 2 Arterial (blue) and venous (red) vessel segmentations following inspiration (**a, c** and **e**) and expiration (**b, d** and **f**) in the same patient. (**a** and **b**) transversal view; (**c** and **d**) coronal view; (**e** and **f**) 3D renderings of the segmented lung vasculature.

distance metric, which is a measure of the curvature of vessels. It is defined by computing the ratio of the length of a curved vessel segment and the length of the arc (straight line) connecting the endpoints of the segment. These values obviously cannot be <1, and the more curved a vessel is, the greater is the value of tortuosity. In addition, lung volume was assessed on inspiration and expiration to standardise the absolute vessel volumes for the size of the lung. In order to assure high data quality, all artery/vein segmentations were visually checked by a board-certified radiologist (TF) and segmentations with <80% correctly labelled vessels were excluded from the analysis.

Data Analysis

Continuous variables are presented as mean and standard deviations (SD), and categorical variables as numbers and/or percentages. Depending on the type of data and number of groups, comparisons were made by the Mann–Whitney *U*-test, Kruskal–Wallis-test, Fisher's exact test, or chi-square test. For the numerical variables FEV_1, RV/TLC and TLCO, the association with predictors was determined by multiple linear regression analysis, whereas the binary variable GOLD D vs ABC was evaluated by multiple logistic regression analysis. Results are given as regression coefficients or odds ratios (OR) with 95% confidence intervals (CI). Mortality was analysed using Cox proportional hazard regression analysis, with the results presented as hazard ratios (HR) and their 95% CI, and with correlations quantified by Pearson's linear correlation coefficients. All regression analyses were performed with corresponding pairs of predictors from inspiration and expiration, thus limiting the problems from collinearity that were otherwise reflected in high values (>5) of the variance inflation factors (VIF). We required complete data on all CT-derived vessel characteristics as well as lung volumes, and also on all clinical and functional data required for the analyses.

For the analysis of vessel volumes, normalised volumes were used to standardise values for lung size. They were obtained by dividing the values of total vessel volume by those of total lung volume, using the data of either inspiration or expiration, and yielding mL per L of lung volume, or one per thousand. To obtain regression coefficients that could be interpreted more easily, tortuosity values were multiplied by a factor of 1000, with the consequence that the regression coefficients also refer to a difference by one per thousand in the respective tortuosity, similar to normalised volumes.

All analyses were performed using the statistical software SPSS (Version 26, IBM, Armonk, New York, USA), and p values <0.05 were considered to be statistically significant.

Results

Study Population

The process of patient selection is illustrated in Figure 1, with the characteristics of the final study population presented in Table 1. In total, 602 patients were included in the sub-study, 138 of whom had complete data. Compared with the excluded patients (ie, those with incomplete data), those included in the analyses were slightly younger and had slightly lower BMI and larger FVC % predicted; they also differed in the GOLD group distribution (Table 1).

Characteristics of Pulmonary Vessels

The arterial and venous volumes and tortuosity at inspiration and expiration, overall and by GOLD grade, are shown in Table 2. Normalised venous volumes at inspiration and expiration, as well as normalised arterial volume and tortuosity at expiration showed statistically significant differences between the different GOLD grades.

Relationship Between Lung Vessel Parameters and Lung Function

Normalised Vessel Volumes

In the linear regression analysis, increasing expiratory ($p = 0.004$) but not inspiratory arterial volume was significantly associated with increasing FEV_1% predicted related to increasing volume (Table 3). Similarly, only normalised expiratory venous volume was significantly ($p < 0.001$) related to increasing FEV_1% predicted ($p < 0.001$, Table 3).

In contrast, for RV/TLC % predicted both expiratory ($p < 0.001$) and inspiratory ($p = 0.018$) arterial volumes were relevant, with the coefficients having opposite signs (Table 3). However, for normalised venous volume, only the expiratory volume was relevant ($p < 0.001$), with a negative relationship to RV/TLC % predicted.

Table 1 Characteristics of the Study Cohort in Comparison with the Patients Who Were Not Part of the Analysis (Ie, Who Participated in COSYCONET at the Time of the SP7 CT Substudy but Either Did Not Participate in SP7, or Had No Valid and/or Sufficient Data)

Variable	Study Cohort n=138	Patients not Included n=1325	p value
Sex (m/f)	61% / 39%	59% / 41%	0.716
Age (y)	64.8 ± 8.7	67.7 ± 8.3	<0.001
BMI (kg/m^2)	26.1 ± 4.7	27.1 ± 5.3	0.041
Pack years	50.3 ± 37.9	44.0 ± 36.8	0.067
Active smoking (yes/no)	24% / 76%	18% / 82%	0.083
FEV_1% predicted	60.5 ± 23.1	57.4 ± 21.6	0.151
FVC % predicted	86.7 ± 20.2	78.3 ± 19.2	<0.001
RV/TLC % predicted	128.6 ± 27.0	131.1 ± 27.7	0.256
TLCO % predicted	60.7 ± 20.9	60.3 ± 23.2	0.878
GOLD grades 0–4	14% / 11% / 41% / 28% / 7%	17% / 7% / 36% / 30% / 10%	0.219
GOLD groups ABCD	51% / 22% / 15% / 12%	44% / 27% / 10% / 19%	0.024

Notes: Mean values and standard deviations, or percentages are given. Comparisons were made by the Mann–Whitney-*U*-test or Fisher's exact test or the chi-square statistics for contingency tables.
Abbreviations: FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV/TLC, ratio of residual volume to total lung capacity; TLCO, transfer factor of the lung for carbon monoxide; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

For TLCO % predicted, only the normalised expiratory arterial and venous volumes ($p = 0.029$ and $p < 0.001$, respectively) were significant predictors, with positive associations between TLCO and volume (Table 3). The results for KCO % predicted were similar (data not shown).

Tortuosity

FEV_1% predicted was associated with expiratory arterial tortuosity ($p = 0.001$) and expiratory venous tortuosity ($p = 0.035$; Table 3). RV/TLC % predicted correlated with expiratory arterial tortuosity ($p = 0.020$) but not with venous tortuosity. TLCO % predicted was again associated with the expiratory arterial tortuosity ($p = 0.003$) and expiratory venous tortuosity ($p = 0.040$). In contrast, there were no significant relationships with inspiratory tortuosity.

Relationship Between Lung Vessel Parameters and GOLD Groups

Normalised Vessel Volumes

When comparing GOLD D (ie patients who have elevated symptoms and are at increased exacerbation risk) with the combined ABC group, the GOLD D group was more likely to have raised normalised inspiratory arterial ($p = 0.030$) and lower normalised expiratory venous ($p = 0.039$) volumes (Table 4).

Tortuosity

Normalised arterial tortuosity upon expiration was (negatively) linked to GOLD D compared to GOLD ABC ($p = 0.041$). There were no associations with venous tortuosity.

Relationship Between Lung Vessel Parameters and Mortality

In order to assess the predictive value of the vessel parameters for clinical outcomes, we analysed the associations between lung vessel parameters following inspiration and expiration with mortality.

Table 2 Mean Values and Standard Deviations of Normalised Vessel Volumes and Tortuosity Derived from CT Scans Performed in Inspiration and Expiration

Variable and CT Condition			All n=138	GOLD 0 n=19	GOLD 1 n=15	GOLD 2 n=56	GOLD 3 n=39	GOLD 4 n=9	p value
Lung volume (L)		Inspiration	6.61 ± 1.46	5.55 ± 1.26	6.28 ± 1.18	6.72 ± 1.41	6.84 ± 1.54	7.64 ± 1.19	0.006
		Expiration	4.74 ± 1.35	3.73 ± 1.08	3.91 ± 0.89	4.7 ± 1.23	5.2 ± 1.24	6.54 ± 1.12	<0.001
Normalised vessel volume	Arterial	Inspiration	13.82 ± 2.46	14.55 ± 2.38	14.44 ± 2.41	13.49 ± 2.41	14.01 ± 2.7	12.44 ± 1.17	0.099
		Expiration	16.85 ± 2.96	17.43 ± 3	18.34 ± 2.79	16.96 ± 3.02	16.49 ± 2.8	14.02 ± 1.17	0.003
	Venous	Inspiration	12.87 ± 2.22	14.46 ± 1.91	13.89 ± 2	12.81 ± 2.16	12.2 ± 2.15	11.1 ± 1.1	<0.001
		Expiration	16.59 ± 3.03	18.36 ± 2.74	19.37 ± 2.86	16.79 ± 2.83	15.18 ± 2.19	13.07 ± 1.4	<0.001
Tortuosity	Arterial	Inspiration	1.01884 ± 0.00317	1.01876 ± 0.00242	1.01968 ± 0.00457	1.01911 ± 0.00351	1.01858 ± 0.00241	1.01713 ± 0.00202	0.418
		Expiration	1.02054 ± 0.0034	1.02165 ± 0.00402	1.02206 ± 0.00374	1.02072 ± 0.0033	1.01967 ± 0.00285	1.01824 ± 0.00255	0.016
	Venous	Inspiration	1.01909 ± 0.00284	1.01892 ± 0.00266	1.01958 ± 0.00396	1.01897 ± 0.00294	1.01923 ± 0.00257	1.0187 ± 0.00178	0.975
		Expiration	1.01988 ± 0.00293	1.0206 ± 0.00337	1.02082 ± 0.00327	1.01976 ± 0.00283	1.01949 ± 0.00278	1.01921 ± 0.00251	0.385

Notes: The p values refer to the comparison of the each of the variables between GOLD grades using the Kruskal–Wallis-test. Normalised vessel volumes were computed as mL of vessel volume per L of lung volume and thus have the unit of per thousand, and tortuosity as a dimensionless indicator of vessel curvature, with the value of one corresponding to a straight line.

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Table 3 Results of Linear Regression Analyses

Variable and CT Condition			FEV_1% Predicted	RV/TLC % Predicted	TLCO % Predicted
Normalised vessel volume	Arterial	Inspiration	−1.978 (−4.330; 0.374) p=0.099	3.260 (0.556; 5.964) p=0.018	0.151 (−1.968; 2.271) p=0.888
		Expiration	2.867 (0.907; 4.826) p=0.004	−4.859 (−7.130; −2.588) p<0.001	1.994 (0.205; 3.783) p=0.029
	Venous	Inspiration	−0.053 (−2.152; 2.045) p=0.960	1.527 (−1.017; 4.071) p=0.237	0.463 (−1.485; 2.411) p=0.639
		Expiration	3.941 (2.403; 5.479) p<0.001	−5.313 (−7.136; −3.490) p<0.001	3.148 (1.684; 4.613) p<0.001
Tortuosity	Arterial	Inspiration	−1.275 (−3.136; 0.587) p=0.178	0.931 (−1.319; 3.182) p=0.414	−0.756 (−2.559; 1.047) p=0.408
		Expiration	2.972 (1.237; 4.707) p=0.001	−2.512 (−4.622; −0.403) p=0.020	2.451 (0.846; 4.055) p=0.003
	Venous	Inspiration	−1.179 (−3.283; 0.926) p=0.270	1.664 (−0.859; 4.186) p=0.194	−1.124 (−3.140; 0.892) p=0.272
		Expiration	2.197 (0.153; 4.241) p=0.035	−1.812 (−4.240; 0.616) p=0.142	1.982 (0.088; 3.876) p=0.040

Notes: Analyses were performed separately for the three lung function variables shown. Each analysis comprised two predictors, namely the inspiratory and the corresponding expiratory value of the respective type of variable, ie arterial or venous normalised vessel volume, or arterial or venous vessel tortuosity. Regression coefficients, their 95% confidence intervals and p values of the coefficients are given. Please note that for better readability and easier interpretation the normalised vessel volumes given in Table 2 in terms of 1:1000 were taken, while the tortuosity values were multiplied by 1000 for analysis. This implies that each of the volume regression coefficients means the change per one of thousand units of the normalised vessel volume, and that each of the tortuosity regression coefficients also refers to a change by one per thousand, thus both corresponding to a difference of 0.1% in the respective predictor.

Table 4 Results of Logistic Regression Analyses for the Distinction Between GOLD D versus ABC, and Cox Proportional Hazard Regression Analyses for Mortality

Variable and CT Condition			Odds ratio for GOLD D vs ABC	Hazard Ratio for Mortality
Normalised vessel volume	Arterial	Inspiration	1.420 (1.035; 1.949) p=0.030	1.391 (0.855; 2.263) p=0.184
		Expiration	0.825 (0.624; 1.090) p=0.176	0.538 (0.337; 0.857) p=0.009
	Venous	Inspiration	1.171 (0.851; 1.611) p=0.333	1.090 (0.641; 1.854) p=0.750
		Expiration	0.756 (0.579; 0.986) p=0.039	0.534 (0.337; 0.845) p=0.007
Tortuosity	Arterial	Inspiration	1.208 (0.921; 1.586) p=0.172	1.182 (0.714; 1.957) p=0.516
		Expiration	0.721 (0.527; 0.987) p=0.041	0.518 (0.291; 0.920) p=0.025
	Venous	Inspiration	1.148 (0.859; 1.534) p=0.353	1.415 (1.028; 1.950) p=0.033
		Expiration	0.766 (0.552; 1.063) p=0.111	0.521 (0.308; 0.882) p=0.015

Notes: Each analysis comprised two predictors, namely the inspiratory and the corresponding expiratory value of the respective variable, ie arterial or venous normalised vessel volume, or arterial or venous vessel tortuosity. Hazard ratios, their 95% confidence intervals and their p values are given. Please note that for better readability and easier interpretation the normalised vessel volumes given in Table 2 in terms of 1:1000 were taken, while the tortuosity values were multiplied by 1000 for analysis. This implies that each of the volume regression coefficients means the change per one of thousand units of the normalised vessel volume, and that each of the tortuosity regression coefficients also refers to a change by one per thousand, thus both corresponding to a difference of 0.1% in the respective predictor.

Normalised Vessel Volumes

When using normalized arterial volumes in inspiration and expiration as predictors, normalised expiratory ($p = 0.009$) but not inspiratory arterial volume was negatively related to mortality (Table 4). Similar results were obtained for normalised inspiratory and expiratory ($p = 0.007$) venous volumes.

Tortuosity

Mortality was negatively associated with arterial tortuosity at expiration ($p = 0.025$) but not inspiration (Table 4). In contrast, the correlation coefficients between mortality and venous tortuosity were statistically significant at both expiration ($p = 0.015$) and inspiration ($p = 0.033$), being in opposite directions.

Integrative Analysis of Mortality Using Vessel Parameters

Given the association between vessel parameters and mortality, as well as between mortality and lung function impairment, we used each of the vessel parameters in a Cox regression analysis together with FEV_1% predicted in order to determine whether each parameter had an independent predictive value. Normalised expiratory venous volume ($p = 0.018$) and FEV_1% predicted ($p = 0.028$) were significantly associated with mortality, whereas for arterial volume ($p = 0.092$), only FEV_1% predicted was significantly associated with mortality ($p = 0.007$). When repeating this analysis with tortuosity at expiration, venous tortuosity was no longer significant ($p = 0.083$), although FEV_1% predicted was ($p = 0.003$), whereas in the case of arterial tortuosity, both expiratory tortuosity ($p = 0.031$) and FEV_1% predicted ($p = 0.010$) were significant. It should be noted that for the vessel parameters the directions of associations were the same as in the analyses without FEV_1 (Table 4), while lower FEV_1% predicted was always associated with increased mortality risk.

Comparison of Vessel Parameters with CT-Based Emphysema Parameters

The above-mentioned analyses for lung function parameters (FEV_1, RV/TLC and TLCO % predicted), GOLD groups (D vs pooled ABC) and mortality were repeated after inclusion of mean lung density in inspiration and expiration as an additional variable. In the analyses of FEV_1, RV/TLC and TLCO % predicted, mean lung density in expiration consistently significantly correlated with the lung function parameters ($p < 0.05$ each), both for arterial and venous parameters. There were no associations between mean lung density and GOLD D vs ABC or mortality risk.

Discussion

The present study aimed to characterise the CT-based morphology of pulmonary vessels at inspiration and expiration in patients with COPD. These characteristics included arterial and venous volumes normalised to lung volume, and tortuosity as a measure of vessel curvature. We found that lung function indices of airway obstruction, air trapping, and gas uptake capacity are more consistently correlated with expiratory vessel characteristics than with inspiratory vessel characteristics. For the correlation between vessel volume and lung function, the superiority of expiration over inspiration was most pronounced for the venous volumes, whereas for tortuosity, arterial values appeared to be superior. The presence of severe COPD in terms of the combination of symptoms and exacerbations defined via GOLD group D compared to groups ABC, was also significantly associated with vessel parameters, again predominantly on expiration. Regarding mortality risk, tortuosity and expiratory venous and arterial normalised volumes were also better predictors than their inspiratory counterparts. Indeed, normalised expiratory venous volume was an independent predictor of mortality, distinct from airway obstruction. These findings suggest that expiratory CT scans carry more information on clinically relevant outcomes than the inspiratory scans that are currently typically performed.

CT scans are a recommended tool for phenotyping patients with COPD, with a focus on the presence and degree of lung emphysema.[8] Emphysema is associated with alterations of lung parenchyma that can be quantified via, for example, the classical Hounsfield units. However, the structural alterations associated with COPD comprise changes in the vascular bed of the lung.[14,41,42]

While many studies have addressed pulmonary hypertension as a common feature of COPD[43,44] and characterised the vascular phenotype in COPD, only two previous studies focused on further vascular changes of the pulmonary venous and arterial system. This comprised volumes, numbers, densities, and fractions of vessels, suggesting that vascular

remodelling occurs in the arterial system in the early stages of COPD and in the venous system in advanced stages.[18,45] However, only one study has analysed the relationship between COPD severity and intrapulmonary vascular volume in different lobes upon inspiration and expiration, the results of which emphasised the superiority of expiratory CT scans in predicting COPD severity.[18] This study used imaging software that enabled automated identification of lung lobes and segmentation of lung vessels, airways and walls, with consecutive 3D reconstruction of pulmonary vessels and calculation of airway wall thickness.[18] The software used in our study also determined further morphological parameters (eg tortuosity) enabling us to specifically address the differences between arterial and venous changes in COPD. Structural changes of the vasculature showed up differently in inspiration and expiration. This is relevant, as routine CT scans are mostly performed following inspiration only, although it is known that CT scans under both inspiration and expiration can be clinically helpful to differentiate emphysema and obstruction.[46,47]

We therefore evaluated a range of clinical questions, such as the relationship of vessel characteristics to mortality risk, on both inspiration and expiration, differentiating between arterial and venous volumes, and introducing a measure of vessel curvature into the analysis. We found it of particular interest that venous but not arterial normalised vessel volume was the most relevant parameter, whereas the arteries were more relevant for tortuosity. The relationship to COPD severity in terms of lung function impairment was confirmed, supporting the assumption that associations of lung function with expiratory venous volume were valid and not a chance finding due to the relatively small sample size. Our data suggest that in patients with COPD in whom an expiratory CT has been performed, the automated analysis of vessel characteristics provides information on mortality risk beyond that contained in spirometric lung function.

The segmentation of pulmonary vessels was performed automatically by pulmonary vessel analysis software developed in-house, yielding volumes, density, and tortuosity of vessels in addition to well-established radiological COPD indices such as lung volume, mean lung density and emphysema index. Of these, we used lung volume to standardise vessel volumes, which were therefore expressed as mL per L of lung volume. It turned out that this normalisation was essential, especially following expiration. The other well-established CT indices that are usually determined on inspiration were not included in our analyses, as their clinical and predictive value in COPD is well known.[48–50] When introducing mean lung density as an additional predictor, lung density following expiration dominated the association with lung function variables, although was not associated with GOLD D or mortality. It should be emphasised that we omitted these parameters in order to directly compare results between inspiration and expiration, and between venous and arterial vessels. The importance of lung density is understandable when considering the limited resolution of CT scans regarding smaller vessels (ie with diameters <2 mm), as it is possible that such vessels are detected only by the density and not vessel analyses. Given these limitations, our data are not sufficiently detailed to disentangle the complexity of the relationship between vasoconstriction, remodelling and destruction in lungs affected by COPD. In contrast to the previous study that quantitatively assessed pulmonary vasculature in COPD,[18] we hypothesised that it would be potentially informative to differentiate between venous and arterial vessels, since these vessels, due to their different stiffness, might behave differently following inspiration and expiration. The same assumption applied to their shape for which tortuosity provides an indicator that could be seen as a measure of curvature. Further, while other groups showed structural changes of the airways in COPD, eg quantified with fractal dimension, the current algorithm did not provide an airway segmentation in sufficient detail to perform analyses on it. Also, the restriction to vessels with 2 to 10 mm diameter, for which we have a high confidence in their accurate detection, would allow only a very rough estimate of their fractal dimension and was hence also not considered.[51–53]

The observed associations showed interesting directions in terms of the regression coefficients. Higher normalised venous vessel volumes upon expiration were linked to better lung function in terms of obstruction, air trapping and gas uptake. Better lung function was also linked to higher values of arterial tortuosity. Regardless of statistical significance, it is also interesting that the regression coefficients on inspiration and expiration always showed opposite signs (Table 3). The direction of the odds ratios for GOLD D vs GOLD ABC and the hazard ratios for mortality were consistent with these findings. Regarding expiratory venous volumes, ratios were <1, indicating that higher normalised volume was associated with lower risk, as was the case for tortuosity upon expiration.

A relatively smaller venous vessel volume at expiration might be linked to a more pronounced collapse of vessels and/or decreased visibility in CT scans, as a sign of more severe lung disease, which, in turn, is typically associated with

impairments in the functional and clinical dimensions of COPD analysed in this study. An additional factor could be the rarefaction of pulmonary vessels that is a key finding in COPD pathophysiology.[6] When comparing GOLD grades 1 and 4 (Table 2), the mean difference in normalised vessel volumes was more pronounced for venous than arterial volume (5.3 vs 3.4 mL per L lung volume). It is not clear whether this is due to different visibility on scans or different rates of degradation or conversion of vessels.[54] Interestingly, the differences in CT-based lung volume between GOLD grades 1 and 4 were 1.36 L following inspiration and 2.63 L following expiration, indicating a larger effect of normalisation in the expiratory than inspiratory scans. It was, however, not possible to use absolute vessel volumes as they depended heavily on lung volume and anthropometric characteristics. We do not have a full explanation for the observation that venous volume but arterial tortuosity was most informative upon expiration, but it is likely due to differences in stiffness and visibility of vessel walls. It could be speculated that arterial alterations reflect the effects of inflammation, hypoxic vasoconstriction, remodelling, and possibly pulmonary hypertension,[55–58] whereas venous alterations reflect reduced inflow due to the missing arterial bed and compression from elevated intrathoracic pressure, especially due to lung hyperinflation, as has been shown for the left heart.[59–62] Regardless of the physiological and methodological factors involved, our results showing the superiority of expiration over inspiration remain valid.

Our study presents preliminary results on the potential role of the expiratory vascular parameters in predicting lung function and disease severity in COPD. We demonstrated that volumetric segmentation and quantification of pulmonary vessels are feasible methods that can be automatically performed, and that the assessment of vascular parameters following inspiration and expiration could further improve risk stratification of patients with COPD. In our view, further prospective studies should address expiratory vascular parameters, as their determination requires an additional CT scan and thus has to be justified in a cost-efficacy analysis.

Limitations

The study was based on a sub-cohort of COSYCONET, with full CT data at inspiration and expiration available in only 138 patients, and there were some differences regarding disease severity compared to the patients not included. However, the analyses included patients with disease severity ranging from very mild to severe, and the results for GOLD group D showed that this number was sufficient for a meaningful analysis. We did not merge GOLD groups C and D into group E, as we explicitly aimed to investigate patients with both high symptoms and exacerbation risk, based on the known correlation between dyspnoea and vascular alterations.[63] Moreover, most analyses were cross-sectional, which allow only the determination of correlations, not causality. Furthermore, vessel characteristics were averaged over vessels down to a diameter of 2 mm, without differentiation into central versus peripheral. Despite the relatively small sample size, results were consistent especially for the relationship between normalised venous volumes in expiration, lung function, group D and mortality risk, thus making it unlikely that these were mere chance findings, although due to the low sample size and high degree of collinearity between vascular parameters, we did not perform regression analysis using the full set of potential predictors at the same time. Finally, due to the low sample size, we did not include cardiovascular comorbidities or further clinical parameters as predictors in our final analyses.

Conclusion

Using data from the COPD cohort COSYCONET, we compared pulmonary vessel characteristics derived by an automated analysis of low-dose chest CT scans between inspiration and expiration. Expiratory parameters, especially expiratory normalised venous vessel volume, were consistently associated with disease severity – but inspiratory parameters were not. This was true for the functional characteristics of airway obstruction, air trapping and gas uptake capacity, and for clinical characteristics such as a high degree of symptoms and increased exacerbation risk, and mortality, for which normalised expiratory venous volume was an independent predictor in addition to airway obstruction in terms of FEV_1. These results demonstrate that, in patients with COPD, relevant clinical information can be extracted from expiratory CT scans that are not evaluated in routine inspiratory scans.

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The study was based on 2741 patients recruited within the COSYCONET framework (ClinicalTrials.gov, Identifier: NCT01245933). For further information see Karch A, Vogelmeier C, Welte T, Bals R, Kauczor HU, Biederer J, Heinrich J, Schulz H, Glaser S, Holle R et al: The German COPD cohort COSYCONET: Aims, methods and descriptive analysis of the study population at baseline. Respir Med 2016, 114:27–37.

Data Sharing Statement

COSYCONET is an ongoing, long-term, multi-centre observational study and the data of which are not intended to be available without demand. If there is interest in the analysis of specific questions, however, there is a formalised procedure for submitting an application to the study office, which will be evaluated by the steering committee on scientific grounds. There is no limitation to this application except proven expertise in COPD studies.

Ethical Statement

The study protocol was approved by the central Ethical Committee in Marburg (Ethikkommission FB Medizin Marburg) and the respective local Ethical Committees: Bad Reichenhall (Ethikkommission Bayerische Landesärztekammer); Berlin (Ethikkommission Ärztekammer Berlin); Bochum (Ethikkommission Medizinische Fakultät der RUB); Borstel (Ethikkommission Universität Lübeck); Coswig (Ethikkommission TU Dresden); Donaustauf (Ethikkommission Universitätsklinikum Regensburg); Essen (Ethikkommission Medizinische Fakultät Duisburg-Essen); Gießen (Ethikkommission Fachbereich Medizin); Greifswald (Ethikkommission Universitätsmedizin Greifswald); Großhansdorf (Ethikkommission Ärztekammer Schleswig-Holstein); Hamburg (Ethikkommission Ärztekammer Hamburg); MHH Hannover/Coppenbrügge (MHH Ethikkommission); Heidelberg Thorax/Uniklinik (Ethikkommission Universität Heidelberg); Homburg (Ethikkommission Saarbrücken); Immenhausen (Ethikkommission Landesärztekammer Hessen); Kiel (Ethikkommission Christian-Albrechts-Universität zu Kiel); Leipzig (Ethikkommission Universität Leipzig); Löwenstein (Ethikkommission Landesärztekammer Baden-Württemberg); Mainz (Ethikkommission Landesärztekammer Rheinland-Pfalz); München LMU/Gauting (Ethikkommission Klinikum Universität München); Nürnberg (Ethikkommission Friedrich-Alexander-Universität Erlangen Nürnberg); Rostock (Ethikkommission Universität Rostock); Berchtesgadener Land (Ethikkommission Land Salzburg); Schmallenberg (Ethikkommission Ärztekammer Westfalen-Lippe); Solingen (Ethikkommission Universität Witten-Herdecke); Ulm (Ethikkommission Universität Ulm); Würzburg (Ethikkommission Universität Würzburg). The study was performed in accordance with the declaration of Helsinki, and all participants gave their written informed consent.

Consent for Publication

The authors confirm that all the contents in this article can be published.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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