

PULMONARY FUNCTION IN PATIENTS WITH ANCA-ASSOCIATED VASCULITIS

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ABSTRACT. *Background and aim:* Although pulmonary manifestations occur frequently in ANCA-associated vasculitis (AAV), empirical evidence of their impact on pulmonary function is scarce. This study analyzed pulmonary function test (PFT) data from a large cohort of patients with AAV. Results were correlated with findings from diagnostic imaging and disease activity. *Methods:* Data from AAV patients with PFTs performed between 2008 and 2018 were extracted retrospectively from the database of a tertiary vasculitis center. Demographic and disease characteristics, imaging data and follow-up results were assessed and compared to PFT results. *Results:* The final analysis encompassed 147 patients. The mean time between first PFT and follow-up was 7.0 ± 11.0 months. In Granulomatosis with Polyangiitis (GPA), forced expiratory vital capacity (FVC_{ex}, $p < 0.001$), residual volume (RV, $p < 0.001$) and the diffusion capacity of carbon oxide (TLCO, $p = 0.003$) were significantly reduced compared to the reference value of 100% predicted. There was no significant difference between patients with or without pulmonary manifestations. In Microscopic Polyangiitis (MPA), reductions of FVC_{ex} ($p < 0.001$), TLC ($p = 0.005$), and TLCO ($p = 0.003$) were observed. In Eosinophilic Granulomatosis with Polyangiitis (EGPA), total airway resistance (RAW_{tot}, $p = 0.024$) and RV ($p = 0.009$) were significantly elevated and TLCO was reduced ($p = 0.014$). Interstitial lung disease (ILD) is associated with a decline of FVC_{ex} (-15.7% , $p = 0.0028$), TLC (-26.5% , $p < 0.001$), RV (-38.9% , $p = 0.023$) and TLCO (-29.1% , $p = 0.007$). Significant differences were neither detected between first PFT and follow-up examination, nor between patients with active versus inactive disease. *Conclusions:* AAV patients presented with characteristic alterations in PFTs according to their respective pulmonary and/or airway manifestations. These results did not change over time and were independent from vasculitis activity.

KEY WORDS: ANCA-associated vasculitis, pulmonary function test, spirometry, interstitial lung disease

Received: 2 January 2024

Accepted: 22 February 2024

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Introduction

AAV are subtyped into granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). The incidence per year per million people in Germany are 34 (GPA), 13 (MPA), and 0–2 (EGPA), respectively (1,2). As potentially fatal

systemic diseases, virtually all organs can be affected, the broncho-pulmonary compartment being one of the most prominent and most frequent sites affected. In some instances, interstitial lung disease (ILD) is the first presentation of the disease (3). Certain characteristics can be identified for each AAV entity. For example, almost all EGPA patients suffer from eosinophilic asthma, mostly long before symptoms of vasculitis arise. In the later course of the disease, granulomatous inflammatory processes, eosinophilic infiltrates, and rarely diffuse alveolar hemorrhage (DAH) may occur (4). Pulmonary parenchymal manifestations or large airway involvement is more common in GPA (66%) than in MPA (25%) (5,6). Besides infiltrates, pulmonary nodules, mass lesions with and without cavitations, and subglottic or tracheobronchial stenoses are seen in GPA, whereas fibrosing ILD is associated with MPA. DAH affects about a quarter of patients in both GPA and MPA (7).

Pulmonary involvement in patients with AAV is associated with a higher mortality rate and increases the risk of a secondary infection which is one of the major causes of death in the first year after diagnosis (8). With respect to the frequent occurrence of pulmonary manifestations in AAV it is important to understand how pulmonary function is affected. Few published studies examined pulmonary function tests in AAV patients, most of which were limited by sample size and the lack of distinction of the three AAV subtypes (9–11).

The objective of our study was to analyze lung function tests in a large cohort of AAV patients at baseline and follow-up. Additionally, findings of the first PFT were correlated with radiologic imaging and disease activity.

Methods

This retrospective study included data from patients with a diagnosis of AAV based on the 2012 revised Chapel Hill Consensus Definitions and the ACR/EULAR classification criteria of 2022 (12–15) diagnosed and treated in our institution between 2008 and 2018. Other inclusion criteria were the presence of at least one PFT, a minimum age of 16 years, and the absence of other acute pulmonary diseases unrelated to vasculitis. Patients with chronic pulmonary diseases or obesity (defined as a body mass index (BMI) of $> 30 \text{ kg/m}^2$) were eligible when the underlying condition was well controlled

and under a stable treatment. These patients were assessed separately.

All data were collected from the electronic records of the vasculitis center at the medius Kliniken, Kirchheim-Teck, Germany. In addition to the PFTs the data acquisition included demographic information and disease specific clinical parameters.

The study was approved by the Ethics Committee of the Medical Faculty of the Eberhard Karls University of Tübingen (732/2018BO2). All evaluations were in accordance with the LDSG Amendment Act as well as the Declaration of Helsinki.

The PFTs were performed with a Ganshorn PowerCube and encompassed spirometry, body plethysmography, carbon monoxide diffusion capacity, and helium spirometry. Individual parameters included forced expiratory vital capacity (FVC_{ex}), peak expiratory flow (PEF), Tiffeneau-Index (rFEV₁), total airway resistance (RAW_{tot}), total lung capacity (TLC), residual volume (RV), and transfer factor for carbon monoxide (TLCO). Measures are expressed as percentages of predicted values where applicable.

Standard prediction equations were used to calculate the percentage of predicted values (16,17) including a hemoglobin specific correction of the gas exchange parameters. An exception was spirometry, the predictive values of which were based on the 2012 global lung function reference values (18).

To assess the percentage of predicted values in terms of pathology, the lower limit of normal (LLN) and the upper limit of normal (ULN), respectively 5th and 95th percentiles, were given preference over fixed cutoff values (17). The severity classification of ventilatory defect patterns was based on LLN/ULN in combination with corresponding reference values (17). Obstruction was defined by an rFEV₁ $< \text{LLN}$ and classified into severity levels using FEV₁. For restriction TLC $< \text{LLN}$ and vital capacity were used, respectively. Impairment in gas exchange was defined and graded by TLCO. A TLCO $< 85\%$ was defined as pathological. Furthermore, a value of FEV₁/PEF > 10 was considered to indicate upper airway obstruction (19).

Disease activity was assessed with the Birmingham Vasculitis Activity Score (BVAS) version 3 (20).

Chest CT findings were labelled according to the glossary published by Fleischner Society (21). The pattern of interstitial lung disease (ILD) was characterized according to the 2002 classification criteria published by the American Thoracic Society and the

European Respiratory Society (22). Chest CT findings were classified as fibrotic when honeycombing, traction bronchiectasis, and/or hyperdense reticulation were present. Focal fibrotic lesions not fulfilling the definition for a specific pattern such as usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP) or others and describing a post-inflammatory state after a localized inflammation were deemed non-specific. Round, homogeneously hyperdense areas of variable size with well-defined margins were classified as nodules. Areas of zonally increased lung attenuation obscuring the margins of vessels and airways were typed as consolidations.

Data cleansing contained the search for outliers. Their assessment was based on the PFT results in context of concomitant cardiac and pulmonary diseases, vasculitis associated pulmonary involvement, BMI, age, quality of the measurement procedures, imaging findings, previous PFT results, and cooperation of the patient during measurement. Results from test procedures in spirometry, body plethysmography, or diffusion measurement with helium spirometry not fulfilling the quality criteria outlined by the German S2k guideline on standardization of spirometry were excluded from the evaluation (23).

Statistical testing was performed using IBM SPSS Statistics version 27, Illinois, USA, applying a two-sided significance test using the threshold of $p < 0.05$. In the presence of Gaussian distribution, the results were described by mean and standard deviation, whereas in the case of other forms of distribution the median and interquartile range were given.

The one-sample unpaired t test was used to compare PFT of AAV patients with healthy individuals expressed by a reference value of 100%. In the case of skewed data the non-parametric Wilcoxon test was applied. When comparing two subgroups, independent sample t-test or Mann-Whitney-U-test were used. Furthermore, analysis for a relationship between imaging results and PFT was performed using multivariate linear regression with the respective PFT size as dependent variable and the imaging findings as independent variables. In turn, the assessment of PFT development over time was performed using paired t-tests. Finally, correlation analysis was applied to examine associations between disease activity and lung function, while ANOVA was used to assess lung function across more than two subgroups.

Results

Baseline characteristics

Patients were eligible for the study if a diagnosis of AAV fulfilling the 2022 ACR/EULAR classification criteria (24–26) was established and if at least one complete set of PFTs were available.

A total of 322 patients with AAV were identified in our database. 166 were excluded from the analysis due to missing or unavailable PFTs. An additional 9 patients were excluded from the study because of insufficient quality of the PFT, or because of an acute pulmonary disease unrelated to the AAV. The remaining 147 patients were considered eligible for the final analysis. In 43 cases of which, a complete follow-up PFT was performed after a median of 7.0 (IQR 11.0) months after the first PFT and were therefore eligible for the longitudinal analysis.

The study included 81 patients with GPA, 37 with MPA, and 29 with EGPA, with a median disease duration of 8.0 ± 66.0 months since diagnosis. The mean age was 55.8 ± 17.6 (GPA), 66.9 ± 14.3 (MPA), and 55.2 ± 17.1 (EGPA) years. While GPA and MPA patients had positive ANCA status in 90% and 100% of cases, respectively, only 21% of EGPA patients were ANCA positive. At the time of the first PFT, 55 (37%) patients had new onset active disease, 5 (3.4%) were refractory active diseases, 42 (29%) were in remission, and 45 (31%) had experienced a relapse.

Pulmonary manifestations were observed in 62% (N=50) of GPA patients, 54% (N=20) MPA patients, and 66% (N=19) of EGPA patients. Asthma was not considered a separate pulmonary involvement, but a core element of EGPA present in 97% (N=28) of the patients.

Baseline characteristics of the study cohort are shown in Table 1.

Patterns of lung function impairment

A restrictive ventilation disorder was present in 19.5% (17/87) of all AAV patients with the highest prevalence of 35% in patients with MPA (7/20) (Figure 1).

An impairment of TLCO was found in 14 patients with GPA (23%), in 9 patients with MPA (31%), and in 3 patients with EGPA (13%). A ratio of FEV1/PEF > 10 and thus a sign of upper

Table 1. Baseline characteristics and demographic properties.

	GPA	MPA	EGPA
Number of patients	81 (55.1%)	37 (25.2%)	29 (19.7%)
Age [years]	58.2* ± 24.1	73.2* ± 19.0	55.8* ± 20.8
Male: Female	26: 55	11: 26	12: 17
Pathological PFT	57 (70.3%)	29 (78.4%)	22 (75.9%)
Disease duration [months]	34.0* ± 121.0	0* ± 16.0	8.0* ± 32.0
CRP [mg/l]	5.7* ± 22.4	25.6* ± 69.5	3.7* ± 6.5
ESR male [mm]	25.0* ± 42.0	56.0* ± 56.0	13.5* ± 7.5
ESR female [mm]	26.0* ± 37.0	45.0* ± 50.0	25.0* ± 30.5
BVAS	3.0* ± 8.0	7.5* ± 9.0	2.0* ± 6.0
BMI male [kg/m²]	25.0* ± 5.5	25.7* ± 3.6	26.5* ± 4.4
BMI female [kg/m²]	25.9* ± 9.1	24.0* ± 6.5	23.7* ± 9.3
Comorbidities			
None	62 (76.5%)	21 (56.8%)	24 (82.8%)
Cardiac	5 (6.2%)	8 (21.6%)	5 (17.2%)
Pulmonary	12 (14.8%)	6 (16.2%)	0 (0%)
Combined	2 (2.5%)	2 (5.4%)	0 (0%)
Thoracic symptoms			
Dyspnea	21 (25.9%)	10 (27.0%)	10 (34.5%)
Cough	15 (18.5%)	7 (18.9%)	9 (31.0%)
Stridor	4 (4.9%)	0 (0%)	4 (13.8%)
Pain	5 (6.2%)	1 (2.7%)	0 (0%)
AAV manifestations			
General	62 (76.5%)	31 (83.8%)	19 (65.5%)
Skin	18 (22.2%)	4 (10.8%)	8 (27.6%)
Ophthalmologic	17 (21%)	2 (5.4%)	2 (6.9%)
ENT	67 (82.7%)	7 (18.9%)	24 (82.8%)
Cardiac	2 (2.5%)	3 (8.1%)	12 (41.4%)
Abdominal	3 (3.7%)	0 (0%)	3 (10.3%)
Renal	26 (32.1%)	18 (48.6%)	2 (6.9%)
PNS	20 (24.7%)	12 (32.4%)	14 (48.3%)
CNS	7 (8.6%)	5 (13.5%)	1 (3.4%)
Pulmonary	50 (61.7%)	20 (54.1%)	19 (65.5%)
Latest treatment in combination with GCS			
None	23 (31.1%)	18 (48.6%)	8 (32.0%)
CYC	20 (27.0%)	11 (29.7%)	8 (32.0%)
RTX	15 (20.3%)	1 (2.7%)	0 (0%)
MTX	7 (9.5%)	2 (5.4%)	0 (0%)
Other	9 (12.2%)	5 (13.5%)	9 (36.0%)
Pulmonary involvement			
Fibrosis	0 (0.0%)	11 (29.7%)	0 (0.0%)
Nodules	23 (33.8%)	0 (0.0%)	2 (10.0%)
Scarring	16 (23.5%)	9 (28.1%)	1 (5.0%)
Consolidation	9 (13.2%)	8 (25.0%)	6 (30.0%)
Emphysema	11 (16.2%)	8 (25.0%)	6 (30.0%)
Bronchial	2 (2.9%)	8 (23.5%)	0 (0.0%)
Subgl. stenosis	5 (7.1%)	0 (0.0%)	0 (0.0%)
DAH	1 (1.5%)	4 (11.8%)	0 (0.0%)

Abbreviations: CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BVAS: Birmingham vasculitis activity score; BMI: body mass index; ENT: ear-nose-throat; PNS: peripheral nervous system; CNS: central nervous system; GCS: glucocorticoids; CYC: cyclophosphamide; RTX: rituximab; MTX: methotrexate; DAH: diffuse alveolar hemorrhage. Pathological PFT is scored when any value below the lower or above the upper limit of normal (LLN/ULN) in any of the following occurred: FVC_{ex}, FEV₁, rFEV₁, TLC, TLCO or RAW_{tot} > 120% predicted. Depending on the distribution mean value or median (*) was quoted.

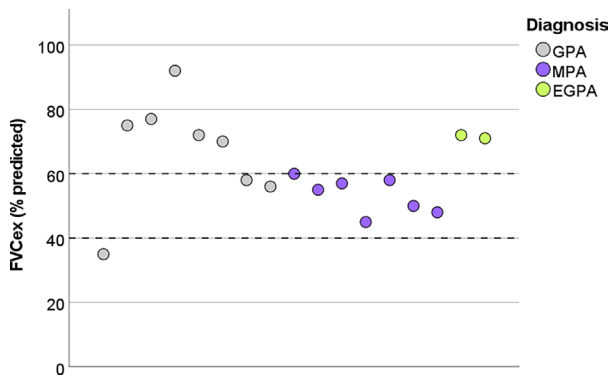


Figure 1. Severity level of restrictive ventilatory defects in patients with AAV. Legend: A restrictive pattern is characterized by TLC below the 5th percentile and classified by FVCex (percent predicted). Severity level ranges from mild (>60%) to moderate (40-60%) and severe (<40%). X-Axis is dimensionless. Each spot marks one patient. Only patients with defined restriction are displayed.

airway obstruction, was observed in a total of 15% of patients (21/137), 81% (17/21) of which were classified as GPA (Figure 1). Absolute numbers differ from the total cohort because not all patients had a complete set of PFT.

Pulmonary function test results based on AAV subtype

In patients with GPA, 57 (70.3%) had pathological PFTs defined as any value deviating more than 20% from the expected LLN or ULN, respectively. FVCex (78.95 ± 15.47 ; $p < 0.001$) as well as TLCO (91.19 ± 22.38 ; $p = 0.003$) were significantly decreased and RV was increased (121.46 ± 31.82 ; $p < 0.001$) compared to the predicted reference value. The PEF (70.40 ± 21.41 ; $p < 0.001$) of GPA patients was the lowest within the AAV cohort. However, there was no significant difference when comparing GPA patients with and without pulmonary involvement (Table 2).

In patients with MPA we detected pathological PFTs in 29 cases (78.4%). In those with ILD, FVCex (64.5 ± 31.0 ; $p < 0.001$), TLC (85.82 ± 21.20 ; $p = 0.005$) and TLCO (87.17 ± 29.11 ; $p = 0.025$) were significantly below normal values. MPA patients with ILD showed a particularly significant decrease in FVCex compared with those without lung involvement (57.0 ± 11.0 vs. 87.0 ± 23.0 ; $p < 0.001$).

Pulmonary function of EGPA was pathological in 22 instances (75.9%). Patients displayed significantly reduced FVCex (70.96 ± 16.12 ; $p < 0.001$) and TLCO (87.0 ± 16.0 ; $p = 0.014$) as well as higher

RAWtot (133.5 ± 88.0 ; $p = 0.024$) and RV (137.0 ± 49.0 ; $p = 0.009$).

Comparing results across GPA, MPA and EGPA, our data showed the most prominent decreases for FVCex, FEV1, TLC and TLCO in MPA patients ($p = 0.005$, $p = 0.002$, $p < 0.001$ respectively) (Table 2).

Pulmonary function test results based on ANCA subtype

To assess the effect of the ANCA subtype on our results we analyzed PFTs for significant changes with respect to ELISA results. In patients with positive PR3 antibodies at the time of PFT FVCex, RV, and TLCO significantly deviated from reference value. Regarding patients with MPO positivity significant changes were observed for FVCex, rFEV1, RAWtot, TLC, and TLCO.

Lung function over time

The mean time between first PFT and follow-up was 7.0 ± 11.0 months. Of the 43 patients who underwent a follow-up, 30 (70%) received a remission induction therapy after the first PFT. At the time of follow-up, 31 subjects (72%) were in remission and 6 (14%) had a relapse. No significant differences between first PFT and follow-up PFT were observed (Table 3). It should be noted that due to the limited sample size, an examination of the three subgroups was not possible.

Lung function in relation to disease activity and imaging patterns on CT

PFT results in relation to disease activity (BVAS) is depicted in Table 4. In most comparisons, there were no significant differences between patients with active compared to those with inactive vasculitis.

For 122 patients (83%) pulmonary imaging studies were performed at the time of the PFT. In most of these cases, a computed tomography (CT) scan (56%; $n = 68$) was performed, followed by a chest X-ray (32%; $n = 39$), CT scan plus X-ray (4%; $n = 5$), and bronchoscopy with any kind of additional radiologic imaging (8%; $n = 10$). We analyzed PFT in the context of various imaging findings using multivariate linear regression (Table 5).

Table 2. Pulmonary function test results.

	PFT Variables	n	Mean ± SD or Median ± IQR	p-value - reference values (100%)	n ₁ n ₂	Mean ± SD or Median ± IQR	p-value - involvement
	GPA	FVC _{ex}	77	78.95 ± 15.47	<0.001**	29 48	79.79 ± 15.63 78.44 ± 15.52
FEV1		78	79.58 ± 16.23	<0.001**	30 48	82.80 ± 18.35 77.56 ± 14.59	0.167
rFEV1		79	100.32 ± 10.31	0.786	30 49	102.13 ± 10.68 99.20 ± 10.03	0.223
PEF		77	70.40 ± 21.41	<0.001**	29 48	69.90 ± 21.94 70.71 ± 21.31	0.873
RAW _{tot}		50	101.5 ± 80.0*	0.252	18 32	95.0 ± 85.0* 101.5 ± 89.0*	0.871
TLC		52	96.60 ± 14.95	0.107	18 34	98.89 ± 15.01 95.38 ± 15.00	0.427
RV		52	121.46 ± 31.82	<0.001**	18 34	121.0 ± 30.0* 118.5 ± 39.0*	0.825
TLCO		62	91.19 ± 22.38	0.003**	24 38	97.00 ± 23.32 87.53 ± 21.26	0.105
MPA		FVC _{ex}	34	64.5 ± 31.0*	<0.001**	15 19	87.0 ± 23.0* 57.0 ± 11.0*
	FEV1	34	72.32 ± 18.75	<0.001**	15 19	90.0 ± 25.0* 58.0 ± 17.0*	<0.001**
	rFEV1	35	103.57 ± 13.78	0.135	16 19	98.5 ± 12.0* 106.0 ± 17.0*	0.230
	PEF	34	73.18 ± 22.62	<0.001**	15 19	75.0 ± 24.0* 70.0 ± 37.0*	0.742
	RAW _{tot}	22	131.5 ± 75.0*	0.016**	9 13	140.0 ± 93.0* 117.0 ± 87.0*	0.102
	TLC	22	85.82 ± 21.20	0.005**	9 13	106,0 ± 13,0* 73,0 ± 29,0*	0,001**
	RV	22	103.00 ± 31.27	0.657	9 13	118.0 ± 29.0* 84.0 ± 53.0*	0.025**
	TLCO	29	87.17 ± 29.11	0.025**	16 13	93.5 ± 28.0* 76.0 ± 42.0*	0.022**
EGPA	FVC _{ex}	26	70.96 ± 16.12	<0.001**	8 18	70.5 ± 34.0* 72.0 ± 27.0*	0,605
	FEV1	27	70.59 ± 19.66	<0.001**	8 18	74.0 ± 34.0* 75.0 ± 35.0*	0,549
	rFEV1	26	96.65 ± 11.08	0.136	8 18	100.0 ± 17.0* 96.0 ± 13.0*	0,724
	PEF	26	75.0 ± 40.0*	<0.001**	8 18	62.0 ± 49.0* 76.5 ± 39.0*	0.935
	RAW _{tot}	18	133.5 ± 88.0*	0.024**	7 11	147.0 ± 67.0* 110.0 ± 110.0*	0.479
	TLC	17	95.47 ± 15.41	0.243	7 10	92.0 ± 32.0* 98.5 ± 21.0*	0.364
	RV	17	137.0 ± 49.0*	0.009**	7 10	104.0 ± 53.0* 141.0 ± 31.0*	0.055
	TLCO	23	87.0 ± 16.0*	0.014**	8 15	86.0 ± 24.0* 87.0 ± 15.0*	0.728

Notes: PFT values are expressed as percentage of predicted. On the left: comparison with reference values (100% predicted). On the right: comparison between patients without (n¹, first row) and with (n², second row) pulmonary manifestation. Depending on the presence of Gaussian distribution one sample t-test or Wilcoxon-test and bidirectional unpaired t-test or Mann-Whitney-U-test with a significance level of = 5% were used for statistical analysis, respectively. Regarding to this mean value or median (*) was quoted. Significant p-values are marked with (**).

Table 3. Comparison of first PFT and follow-up.

PFT values	AAV			
	N	PFT1	Follow-Up	p-value
FVCex	39	74.92 ± 16.21	73.21 ± 14.78	0.383
rFEV1	41	101.29 ± 12.12	102.29 ± 13.18	0.460
RAWtot	18	143.56 ± 65.81	153.72 ± 94.10	0.637
TLC	18	93.50 ± 15.424	93.72 ± 15.785	0.918
RV	18	113.94 ± 27.73	113.67 ± 30.94	0.967
TLCO	29	89.10 ± 24.70	87.62 ± 23.60	0.654

Notes: PFT values are expressed as percentage of predicted. Mean value of first pulmonary function test (PFT1) and Follow-Up. N: Sample size. Bidirectional paired t-test with a significance level of $\alpha = 5\%$ was used for statistical analysis. Significant p-values are marked with (**).

Table 4. Pulmonary function and BVAS status.

PFT	BVAS	GPA			MPA			EGPA		
		N	Mean ± SD or Median ± IQR	p	N	Mean ± SD or Median ± IQR	p	N	Mean ± SD or Median ± IQR	p
FVCex	0 > 0	25	77.00 ± 16.33	0.047**	8	63.0 ± 29.0*	0.817	9	71.0 ± 27.0*	0.293
		52	79.88 ± 15.12		25	63.0 ± 37.0*		17	74.0 ± 28.0*	
rFEV1	0 > 0	26	97.65 ± 11.69	0.108	8	95.5 ± 29.0*	0.371	9	98.0 ± 15.0*	0.978
		53	101.62 ± 9.41		26	105.0 ± 12.0*		17	96.0 ± 15.0*	
RAWtot	0 > 0	15	110.0 ± 80.0*	0.159	5	140.0 ± 155.0*	0.845	6	116.5 ± 112.0*	0.779
		35	87.0 ± 84.0*		17	130.0 ± 66.0*		12	150.0 ± 100.0*	
TLC	0 > 0	16	99.44 ± 17.57	0.366	5	74.0 ± 29.0*	0.290	6	91.0 ± 21.0*	0.119
		36	95.33 ± 13.72		17	93.0 ± 39.0*		11	100.0 ± 23.0*	
RV	0 > 0	16	126.0 ± 25.0*	0.145	5	92.0 ± 36.0*	0.610	6	113.0 ± 44.0*	0.044**
		36	115.0 ± 38.0*		17	104.0 ± 49.0*		11	142.0 ± 44.0*	
TLCO	0 > 0	18	90.5 ± 35.0*	0.858	8	87.5 ± 33.0*	0.541	7	85.0 ± 10.0*	0.269
		44	93.5 ± 26.0*		20	87.5 ± 50.0*		16	92.0 ± 25.0*	

Notes: PFT values are expressed as percentage of predicted. Comparison between patients with (BVAS > 0) and without active vasculitis (BVAS = 0). Depending on the presence of Gaussian distribution bidirectional unpaired t-test or Mann-Whitney-U-test with a significance level of $\alpha = 5\%$ were used for statistical analysis, respectively. Mean values or median (*) are shown. Significant p-values are marked with (**).

Regression models used FVCex, rFEV1, RAWtot, TLC, RV and TLCO as dependent variables and independent variables included diagnosed lung fibrosis (LF), nodules (ND), scarring (SC), consolidation (CL), emphysema (EM), bronchial involvement (BI), subglottic stenosis (ST), and diffuse alveolar hemorrhage (DAH).

No statistically significant effect was found for the models of rFEV1 ($p=0.064$) and RAWtot ($p=0.118$). When LF was present, FVCex, TLC, RV, and TLCO showed decrements of 15.7% to 38.9% from predicted values. In case of scarring, FVCex was reduced by 9.8% (95%CI -17.459; -2.068; $p=0.013$) and TLCO by 13.4% (95%CI -25.005; -1.769; $p=0.024$).

Furthermore, consolidation was associated with -9.9% (95%CI 18.248; -1.473; $p=0.022$) reduced values for FVCex and -15.4% (95%CI -24.636; -6.249; $p<0.001$) for TLC. Regression analyses revealed no significant findings regarding bronchial involvement, emphysema, subglottic stenosis, and DAH.

Except for significantly impaired TLC ($p=0.019$) and RV ($p<0.001$) for patients with a BMI > 30 kg/m² there were no substantive changes in the model parameters as presented in Table 5 when potential confounders such as obesity, and pulmonary and cardiovascular co-morbidities were added to the models. Therefore, these factors were excluded from the final analysis presented in Table 5.

Table 5. PFT in the view of diagnostic imaging/endoscopy.

		B [95%-CI]	β	p-value	n	R ²	F-statistics
FVC _{Cex}	C	80.031 [75.826; 84.235]			110	0.171	<0.001**
	LF	-15.656 [-29.550; -1.761]	-0.246	0.028**			
	ND	1.125 [-6.290; 8.539]	0.027	0.764			
	SC	-9.764 [-17.459; -2.068]	-0.240	0.013**			
	CL	-9.861 [-18.248; -1.473]	-0.232	0.022**			
rFEV1	C	100.717 [97.688; 103.746]			113	0.062	0.064
	LF	10.949 [0.941; 20.957]	0.250	0.032**			
	ND	-1.628 [-6.969; 3.712]	-0.058	0.547			
	SC	0.804 [-4.739; 6.346]	0.029	0.774			
	CL	-1.288 [-7.329; 4.754]	-0.044	0.673			
RAW _{tot}	C	126.966 [109.248; 144.684]			76	0.068	0.118
	LF	-37.394 [-96.001; 21.212]	-0.179	0.207			
	ND	-43.677 [-74.950; -12.404]	-0.323	0.007**			
	SC	27.325 [-5.133; 59.783]	0.205	0.098			
	CL	11.512 [-23.867; 46.890]	0.082	0.518			
TLC	C	100.002 [95.398; 104.607]			77	0.341	<0.001**
	LF	-26.478 [-41.709; -11.248]	-0.407	0.001**			
	ND	-1.892 [-10.019; 6.235]	-0.045	0.644			
	SC	-6.799 [-15.234; 1.636]	-0.164	0.112			
	CL	-15.442 [-24.636; -6.249]	-0.356	0.001**			
RV	C	125.697 [115.580; 135.814]			77	0.129	0.024**
	LF	-38.919 [-72.382; -5.456]	-0.313	0.023**			
	ND	-4.231 [-22.087; 13.625]	-0.053	0.638			
	SC	1.525 [-17.008; 20.058]	0.019	0.870			
	CL	-10.786 [-30.986; 9.415]	-0.130	0.290			
TLCO	C	96.928 [90.583; 103.274]			93	0.180	0.001**
	LF	-29.094 [-50.072; -8.117]	-0.328	0.007**			
	ND	2.507 [-8.687; 13.700]	0.044	0.657			
	SC	-13.387 [-25.005; -1.769]	-0.237	0.024**			
	CL	-9.065 [-21.729; 3.598]	-0.153	0.158			

Notes: PFT values are expressed as percentage of predicted. Constant (C), lung fibrosis (LF), nodule (ND), scarring (SC), consolidation (CL). Included in each model but not displayed: emphysema, bronchial involvement, stenosis, and diffuse alveolar hemorrhage. Statistical method: Multivariate linear regression. B = regression coefficient (95%-CI), β = standardized coefficient, n = sample size per model, R² = adjusted correlation coefficient, F-statistics per model. Significant results are printed in bold and marked with (**).

Discussion

In this study we investigated PFTs in AAV patients at two timepoints and correlated our findings with disease activity, AAV subtype and radiographic changes.

Our data suggests that most patients with AAV have normal PFTs even when pulmonary manifestations are present, since we detected pathological measurements in only 24-30% of patients. The leading patterns of PFT alterations was upper airway obstruction in GPA, restrictive ventilation disorders

Table 6. Studies on lung function in AAV.

	N	Diagnosis	FVC	TLC	TLCO
Hozumi et al. [7]	84	MPA-ILD	85 ± 17	<i>n.a.</i>	74 ± 21
Rosenberg et al. [21]	22	GPA	75 ± 8	81 ± 7	74 ± 12
Newall et al. [14]	15	GPA + MPA	67	102	88
Koldingsnes et al. [10]	57	GPA	<i>n.a.</i>	67	55
Present publication	81	GPA	79 ± 15	97 ± 15	91 ± 22
	37	MPA	65 ± 31	86 ± 21	87 ± 29
	29	EGPA	71 ± 16	95 ± 15	87 ± 16

Comparison of PFT data between our study and other published studies. PFT values are expressed as percentage of predicted. FVC = forced vital capacity, TLC = total lung capacity, TLCO = transfer factor for carbon monoxide.

in MPA and an increase in total airway resistance in EGPA patients.

It is noteworthy, that in our GPA cohort, PFT alterations did not discriminate patients with pulmonary involvement from those without, which is consistent with findings of other authors (10). First, it has to be noted that the most common pulmonary manifestations in GPA such as granulomatous lesions, nodules and cavities are focal lesions, which have a lesser or no impact on lung function compared to diffuse parenchymal changes such as DAH and ILD (27). Furthermore, the fraction of smokers amongst our GPA patients was 75%, which is overproportionate compared to 55% in the entire collective. We suspect this to be a major cause for the reduction in TLCO in our pulmonary and non-pulmonary GPA patients. Only one GPA patient had emphysema and another silicosis, both of which did not affect the results significantly. There were no suspected cases of pulmonary embolism or pulmonary hypertension in our patients. It remains speculative whether very early pulmonary capillaritis, which might not be detected by imaging but already affected diffusion capacity, played an additional role. On the other hand, pulmonary capillaritis with DAH typically causes false-high CO-diffusion results by direct binding of inhaled CO by free intraalveolar hemoglobin which could have added to the lack of discrimination (28).

A FEV1/PEF > 10 suggesting upper airway obstruction was detected in 22% of our GPA patients, but in only 5 patients a definite diagnosis of tracheal or (sub)glottic stenosis was made by endoscopy or ENT inspection. It has been shown that standard chest CT is inferior to dynamic CT imaging modalities in detecting subglottic stenosis or tracheo-bronchomalacia (29,30). Therefore, it is possible that

subclinical upper airway lesions may have been overlooked in some instances.

The prevalence of ILD in MPA patients is high and ranges between 10 and 60% in the literature (31,32). Accordingly, most patients with fibrosing ILD and restrictive ventilation disorders in our cohort were MPO-positive AAV patients. The extent of the functional impairment in PFTs (FVC and TLCO) of our MPA cohort was comparable to the reports of Hozumi and Newall (10,31) (Table 6). Unlike in GPA, PFT discriminates MPA patients with ILD disease manifestations from those with purely extra-pulmonary disease. Compared to GPA and EGPA, MPA patients in our study most commonly displayed a restrictive ventilatory pattern. Only very few studies compared PFTs of AAV subtypes with each other. In contrast to our results, Newall et al. found the lung function of GPA patients to be worse than those with MPA (10).

In EGPA patients, we found an increased total airway resistance while changes in rFEV1, counter-intuitively, were not statistically significant. Bronchial asthma, an almost obligatory feature of EGPA, usually precedes the diagnosis of vasculitis for many years. Consequently, nearly 75% of all our EGPA patients were on asthma medications at the time of diagnosis, which likely affected the detection of airway obstruction in PFTs when performed if the patients' asthma was well controlled. The effect of immunosuppressive therapy on airway obstruction in EGPA may be an additional contributor to asthma control in these patients.

When evaluating our results regarding ANCA subtype, there were no major deviations compared to the analysis when the cohort was divided by clinical AAV type. This was due to a large overlap between

diagnosis and ANCA subtype: Almost every PR3-ANCA positive patient belonged to the GPA cohort (98%; N=44), whereas the majority of patients with MPO-ANCA had a clinical diagnosis of MPA (81%; N=30).

Since there were no correlations between PFTs and disease activity based on BVAS, we subsequently did not find significant changes in the follow-up PFTs even though the number of patients in remission increased from 21 to 67% between the two points in time. Other authors (analyzing GPA patients only) found improvements in PFT under therapy (9,11). Then again, our GPA patients' lung function tests did not reliably reflect the presence of pulmonary involvement in the first place which makes a change under treatment not very likely. ILD and pulmonary fibrosis with restriction being the dominant finding in our MPA cohort are often also not subject to rapid changes. It is conceivable that a longer time interval between initial and follow-up PFT might yet unmask improvements or deteriorations in the case of ILD during longer follow-up.

To our knowledge, with 147 patients this study is the largest report on lung function in patients with AAV to date. However, there are limitations related to its retrospective design. An indication bias must be assumed due to the fact that patients with pulmonary manifestations probably underwent PFT more often. Furthermore, a single center study is prone to a referral bias. Our analysis of follow-up data was limited in its validity by the necessity of pooling all three subtypes due to low numbers and by the short time interval to the follow-up PFT. Because we did not have radiological imaging data for the time of follow-up, it was not possible to compare any alterations in PFT to morphological changes at that point. Moreover, our study does not provide clinical functional data such as a 6-minute walk test results. We do not provide for sufficient data to assess effects of immunosuppressive therapy on lung function.

Although possible confounders like chronic pulmonary and cardiovascular diseases as well as obesity did not show a statistical impact on PFT, they might have influenced our results to a certain extend.

Despite these methodological limitations, our work adds to the knowledge on lung function in AAV patients, which warrants further prospective investigations.

Conclusion

Each AAV subtype presents with a characteristic pattern of lung function impairment: In GPA, lung function is rarely impaired, but extra-thoracic obstruction due to subglottic airway stenosis can occur. MPA patients show diffusion impairment as well as restriction, in particular those with lung fibrosis. In EGPA an obstructive pattern is detected only in a fraction of patients and rFEV1 may be unaffected.

Pulmonary function is impaired in a significant proportion of AAV patients and, therefore, PFT should be included to the diagnostic work-up at diagnosis and, in selected cases (e.g. with impaired PFT and/or pulmonary disease at diagnosis), also for follow-up.

Abbreviations: AAV: ANCA-associated vasculitis; ANCA: Antineutrophil cytoplasmic antibody; ANOVA: Analysis of variance; BI: Bronchial involvement; BVAS: Birmingham Vasculitis Activity Score; C: Constant; CL: Consolidation; CT: Computed tomography; DAH: Diffuse alveolar hemorrhage; EGPA: Eosinophilic granulomatosis with polyangiitis; ELISA: Enzyme-linked immunosorbent assay; EM: Emphysema; ENT: Ears-nose-throat; F1: First Follow-Up; FEV1: Forced expiratory volume in 1 second; FVCex: Forced vital capacity (expiratory); GPA: Granulomatosis with polyangiitis; IQR: Interquartile range; PFT: Pulmonary function test; LF: Lung fibrosis; LLN: Lower limit of normal; MPA: Microscopic polyangiitis; ND: Nodule; PEF: Peak Expiratory Flow; PFT: Pulmonary function test; RAWtot: Total airway resistance; rFEV1: Tiffeneau-Index; RV: Residual volume; SC: Scarring; SD: Standard deviation; ST: Subglottic stenosis; TLC: Total lung capacity; TLCO: Transfer factor for carbon monoxide; ULN: Upper limit of normal; VC: Vital capacity; VCin: Vital capacity (inspiratory).

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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