Dissertation

Early recognition of pulmonary vascular changes with exercise right heart catheterization in patients with COPD

submitted by

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Statutory Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the "Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz".

Date: 13.08.2023 *Teresa Sassmann, eh.*

Disclosures

Abstracts from this work were presented at national and international conferences. Parts of the results were published as full paper in December 2022 in Respiratory Research (PMID: 36482405) [1] with the following title:
Abnormal pulmonary hemodynamics during exercise is associated with exercise capacity in COPD

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Abstract

Background and aims: Chronic obstructive pulmonary disease (COPD) is frequently complicated by pulmonary hypertension (PH), which is accompanied with exercise limitation and poor outcome. We hypothesized that even COPD patients without relevant resting PH are limited by pathological pulmonary hemodynamics during physical activity.

Methods: We retrospectively analyzed consecutive COPD patients with resting mean pulmonary arterial pressure (mPAP) < 25 mmHg and compared them to age- and sex-matched controls without chronic pulmonary disease. All patients underwent clinical work-up including clinically indicated invasive hemodynamic assessment at rest and during exercise. Chi-square tests were performed for categorical variables and Fisher's exact test or Mann-Whitney-U-tests for continuous data. With Spearman rank correlation tests, associations were analyzed.

Results: 26 patients with COPD (female/male: 16/10, 66±11yr, FEV1: 56±25 %predicted) and 26 age- and sex-matched controls (FEV1: 96±22 %predicted) were analyzed. COPD patients presented with slightly increased mPAP (21 (18-23) vs. 17 (14-20) mmHg, p=0.022), pulmonary vascular resistance (PVR) (2.5 (1.9-3.0) vs. 1.9 (1.5-2.4) WU, p=0.020) at rest compared to controls. During exercise, COPD patients had higher mPAP (47 (40-52) vs. 38 (32-44) mmHg, p=0.015) and PVR (3.1 (2.2-3.7) vs. 1.7 (1.1-2.9) WU, p=0.028) and lower individual peak work load (50 (50-75) vs. 100 (75-125) Watt, p=0.002). Compared to controls, the mPAP/cardiac output slope was significantly increased in COPD patients (6.9 (5.5-10.9) vs. 3.7 (2.4-7.4) vs.) mmHg/L/min, p=0.007) and negatively correlated with both 6-minute walk test (r=-0.46, p=0.001) and peak oxygen uptake (r=-0.46, p=0.007).

Conclusion: Even COPD patients presenting with mild elevation of pulmonary arterial pressure and resistance, show exercise pulmonary hemodynamics with a strongly increased mPAP/CO-slope, limiting their exercise capacity.

Zusammenfassung

Grundlagen und Ziele: Die individuelle Belastbarkeit und die Mortalität wird bei PatientInnen mit chronisch obstruktiver pulmonaler Erkrankung (COPD) durch das Vorliegen einer pulmonalen Hypertonie aggraviert. Ziel dieser Arbeit ist die pulmonale Belastungshämodynamik von COPD PatientInnen ohne relevante PH in Ruhe zu evaluieren.

Methoden: PatientInnen mit COPD und mittleren pulmonal arteriellen Druck (mPAP) <25 mmHg wurden retrospektiv analysiert und mit Alters- und Geschlechts gematchten Kontrollen ohne Lungenerkrankungen verglichen. Neben Routineuntersuchungen erhielten alle eine klinisch indizierte invasive Ruhe- und Belastungs-Rechtsherzkatheteruntersuchung. Gruppenunterschiede wurden mit dem Chi-Quadrat Test bzw. Fisher's exakten Test oder Mann-Whitney-U-Tests untersucht. Korrelationen wurden mit dem Spearman Rang Korrelationstest ausgeführt.

Ergebnisse: 26 COPD PatientInnen (Frau/Mann: 16/10, 66±11yr, FEV1: 56±25 %Soll) und 26 alters- und Geschlechts gematchte Kontrollen (FEV1: 96±22 %predicted) wurden analysiert. Während COPD PatientInnen im Vergleich zu den Kontrollen in Ruhe lediglich einen leicht erhöhten mPAP (21 (18-23) vs. 17 (14-20) mmHg, p=0.022) und pulmonalen Gefäßwiderstand (PVR) (2.5 (1.9-3.0) vs. 1.9 (1.5-2.4) WU, p=0.020) aufwiesen, war der Unterschied während Belastung deutlich ausgeprägter (mPAP (47 (40-52) vs. 38 (32-44) mmHg, p=0.015) und PVR (3.1 (2.2-3.7) vs. 1.7 (1.1-2.9) WU, p=0.028)), obwohl die Spitzenbelastung geringer war (50 (50-75) vs. 100 (75-125) Watt, p=0.002). Der mPAP/cardiac output slope war bei den COPD PatientInnen signifikant erhöht (6.9 (5.5-10.9) vs. 3.7 (2.4-7.4) mmHg/L/min, p=0.007) und korrelierte mit dem 6-Minuten Gehtest (r=-0.46, p=0.001) und der maximalen Sauerstoffaufnahme (r=-0.46, p=0.007).

Schlussfolgerungen: Auch ohne relevante Ruhe-PH zeigen COPD PatientInnen charakteristische Veränderungen der pulmonalen Hämodynamik unter Belastung, was potentiell einen wichtigen Faktor der Belastungseinschränkung darstellt.

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Abbreviations and Definitions

6MWT	Six-minute-walk test
AaDO2	alveolar-arterial oxygen gradient
BMI	Body mass index
bzw.	Beziehungsweise
CAT	COPD Assessment Test
CI	Cardiac index
CO	Cardiac output
COPD	Chronic Obstructive Pulmonary Disease
CpcPH	Combined post- and pre-capillary pulmonary hypertension
CPET	Cardiopulmonary exercise testing
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
DLCOcSB	Diffusing capacity of lung for carbon monoxide single breath
DLCOcVA	Diffusing capacity of lung for carbon monoxide for alveolar volume corrected for hemoglobin
dPAP	Diastolic pulmonary arterial pressure
E	Early diastolic filling velocity
e.g.	Example given
E'	Early diastolic myocardial velocity
ECG	Electrocardiography
$FECO_2$	Fraction of exhaled CO2
FEV1	Forced expiratory volume in the first record of expiration
FVC	Forced vital capacity
GFR	Glomerular filtration rate
GOLD	Global Initiative for Chronic Obstructive Lung Disease
Hb	Hemoglobin
Hct	Hematocrit
ILD	Interstitial Lung Disease
IpcPH	Isolated post-capillary pulmonary hypertension
IQR	Interquartile range
K	Potassium
L	Liter
LTOT	Long-term oxygen therapy
LVEF	Left ventricular ejection fraction
mHz	Megahertz
min	Minute
ml	Millilitre
mmHg	Millimetres of mercury
mMRC	Modified Medical Research Council
mPAP	Mean pulmonary arterial pressure
mPAP	Mean pulmonary artery pressure
n.s.	Not significant

NTproBNP	N-terminal pro brain natriuretic peptide
NYHA	New York Heart Association
PAH	Pulmonary Arterial Hypertension
PAWP	Pulmonary artery wedge pressure
pCO2	Carbon dioxide partial pressure
PH	Pulmonary hypertension
pO2	Oxygen partial pressure
PVC	Pulmonary vascular compliance
PVD	Pulmonary vascular disease
PVP	Pulmoary vascular phenotype
PVR	Pulmonary vascular resistance
py	Pack years
RAP	Right atrial pressure
RHC	Right heart catheterization
RVOR	Right ventricular output reserve
s'	Peak systolic right ventricular velocity
sPAP	Systolic pulmonary arterial pressure
TAPSE	Tricuspid annular plane systolic excursion
TLC	Total lung capacity
TPR	Total pulmonary resistance
TRV	Tricuspid regurgitation velocity
VCI	Inferior vena cava
VO2	Oxygen uptake
vs.	Versus
WHO-FC	World Health Organization functional class

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1 Introduction

The pulmonary circulation is characterized by low resistance and small pressure difference. The walls of the vessels are thinner and have less smooth muscle cells compared to vessels of the systemic arterial circulation. Therefore, vessels can expand very much dependent on the hydrostatic- and the alveolar space pressure. As soon as pulmonary arterial pressure increases, flow resistance decreases and non-perfused vessels are recruited. Consequently, cardiac output rises. On the other hand, alveolar hypoxia leads to increase in pulmonary flow resistance and decrease in local perfusion (hypoxic vasoconstriction). With these two mechanisms lung perfusion is regulated.

The right ventricle (RV) is a muscle that is accustomed to resting systolic pressures of approximately 20 mmHg. Various conditions like e.g. left heart diseases, pulmonary diseases, pulmonary vascular disease, or chronic thromboembolic disease lead to chronic significant increase in afterload and RV strain. At the onset of pulmonary hypertension (PH), the RV tries to adapt to increasing pulmonary arterial pressures. At that initial stage the pulmonary artery to right ventricular (PA-RV) coupling is preserved. With further increase in PA pressure, RV fails at a certain point. PA-RV uncoupling is the consequence, ultimately leading to right heart failure and death [2,3].

Nowadays because of its predominant irreversible, exercise limiting and life-threatening character many efforts are undertaken to diagnose pulmonary hypertension, before right heart failure occurs. This work focusses on early recognition and clinical relevance of pulmonary vascular changes in COPD patients.

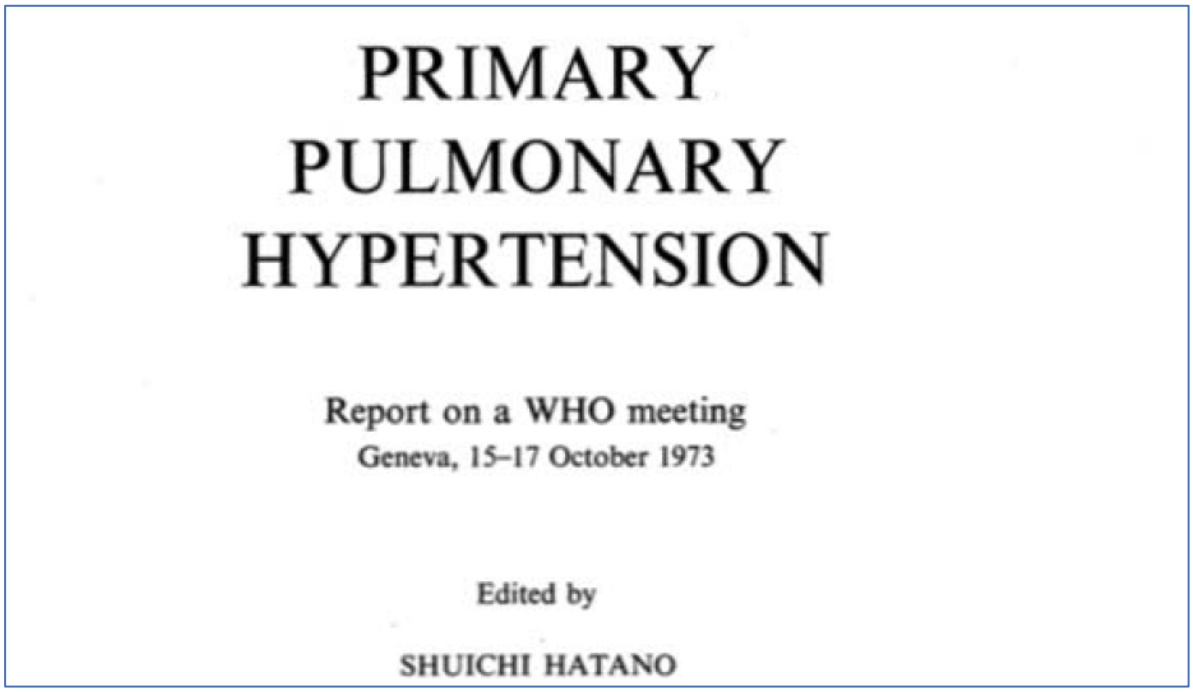
Within this chapter the hallmarks of pulmonary hypertension will be recapitulated finally leading to our research question.

1.1 Pulmonary Hypertension

Approximately 1% of the global population suffers from PH, which is a complex pathophysiological disorder leading to increased pulmonary arterial pressure. The genesis is multifactorial and diagnosis, treatment, and management of these patients often require a multidisciplinary team in an expert center. Every group of age can be affected, however prevalence in older subjects is higher, predominately due to pulmonary and left heart diseases. Irrespective of its etiology PH is associated with poor outcome. Due to its complex character many aspects of PH are still unclear and controversial discussed [2,4].

1.1.1 Definition of pulmonary hypertension

Since the first World Symposium on Pulmonary Hypertension (WSPH) in 1973 in Geneva PH was defined by an elevation of mean pulmonary arterial pressure (mPAP) above 25 mmHg for many decades, although it was initially stated by Hatano et al. that under physiological conditions a resting mPAP almost never exceeds 20 mmHg in a healthy person [5,6].


PRIMARY
PULMONARY
HYPERTENSION

Report on a WHO meeting
Geneva, 15–17 October 1973

Edited by

SHUICHI HATANO

Figure 1 Cover of the First World Symposium on PH held 1973 in Geneva, Switzerland [5]

In 2015 Galiè et al. changed this cut-off to ≥ 25 mmHg, but still clinical relevance of so called "borderline PH" with a mPAP between 21-24 mmHg was unclear. Numerous studies were performed to investigate what should be considered a normal mPAP and if a resting mPAP in the borderline range has a clinical impact. In 2009 Kovacs et al. found in a large meta-analysis that mPAP of healthy persons is 14.0 ± 3.3 mmHg (mean ± SD) and thereby confirmed a mPAP of 15 mmHg as normal, which was stated at the 1st WSPH [5,7]. Further studies reported a reduced exercise performance, an increased mortality and an elevated risk to PAH progress in subjects within the borderline mPAP region [8–11]. Consequently, in the recently published ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension the mPAP cut-off for defining PH was reduced to >20 mmHg.

Furthermore, pulmonary vascular resistance (PVR) and pulmonary arterial wedge pressure (PAWP) contribute to the differentiation between pulmonary vascular disease (PVD) and PH due to left heart disease. Current definition of pre-capillary PH, post-capillary PH and combined pre-and postcapillary PH are summarized in Table 1.

Definition	Hemodynamic characteristics
Pre-capillary pulmonary hypertension	mPAP >20 mmHg PAWP ⩽15 mmHg PVR >2 WU
Isolated post-capillary pulmonary hypertension (IpcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR ⩽2 WU
Combined post- and pre-capillary pulmonary hypertension (CpcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU

Table 1 Hemodynamic definition of PH [2]

Of note, post-capillary PH summarizes all conditions causing PH due to an increase in PAWP, in the majority of cases due left heart diseases. On the other hand, pre-capillary PH includes increased pulmonary arterial pressure and resistance due to multiple changes predominantly directly affecting the pulmonary arteries, capillary system or veins in the case of pulmonary venoocclusive disease. Combined forms can occur in any phenotype, especially in patients with multiple comorbidities. Based on recently published studies PVR was determined as prognostically relevant when exceeding 2 Wood units (WU) [12,13]. This definition thereby also changed in this current guideline, as until then the threshold for PVR was >3 WU [6].

1.1.2 Classification of pulmonary hypertension

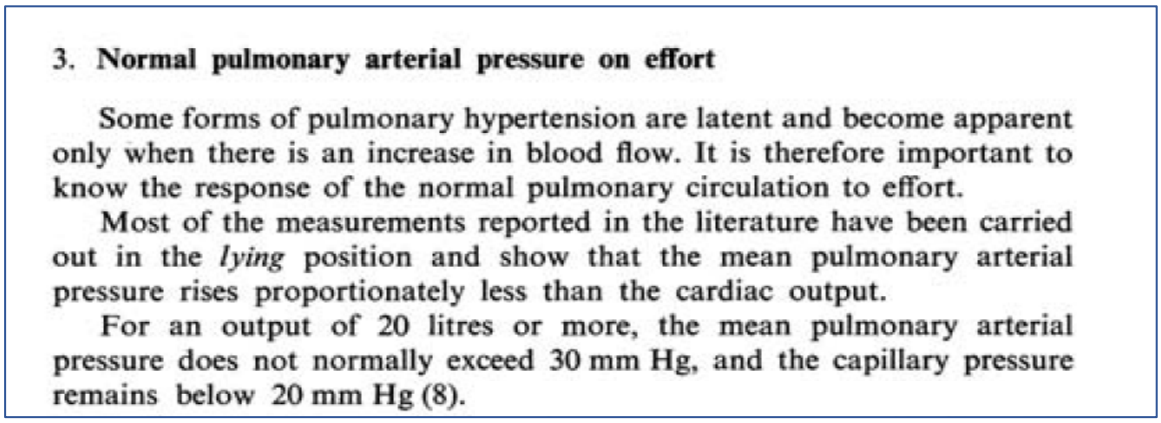
Since PH was introduced in 1973, the classification has changed several times. The original classification differentiated between primary and secondary types of PH. Primary PH was defined as PH due to conditions primarily affecting pulmonary arteries. The term secondary PH was used for any other condition outside the pulmonary arteries leading to PH. In 1998 a new classification system was introduced at the 2nd WSPH also including pathophysiological mechanisms, clinical features, and therapeutic options. This structure was only slightly changed over the following decades until the today's recommendations for classification system were established (Table 2). It is stated that although hemodynamics are crucial for characterizing PH, the final diagnosis should be based on the whole clinical context and performed investigations [2,5].

Clinical classification of pulmonary hypertension	
GROUP 1 Pulmonary arterial hypertension (PAH)	1.1 Idiopathic 1.1.1 Non-responders at vasoreactivity testing 1.1.2 Acute responders at vasoreactivity testing 1.2 Heritable 1.3 Associated with drugs and toxins 1.4 Associated with: 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement 1.6 Persistent PH of the newborn
GROUP 2 PH associated with left heart disease	2.1 Heart failure: 2.1.1 with preserved ejection fraction 2.1.2 with reduced/mildly reduced ejection fraction 2.2 Valvular heart disease 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH
GROUP 3 PH associated with lung diseases and/or hypoxia	3.1 Obstructive lung disease or emphysema 3.2 Restrictive lung disease 3.3 Lung disease with mixed restrictive/obstructive pattern 3.4 Hypoventilation syndromes 3.5 Hypoxia without lung disease (e.g. high altitude) 3.6 Developmental lung disorders
GROUP 4 PH associated with pulmonary artery obstructions	4.1 Chronic thrombo-embolic PH 4.2 Other pulmonary artery obstructions
GROUP 5 PH with unclear and/or multifactorial mechanisms	5.1 Hematological disorders 5.2 Systemic disorders 5.3 Metabolic disorders 5.4 Chronic renal failure with or without hemodialysis 5.5 Pulmonary tumor thrombotic microangiopathy 5.6 Fibrosing mediastinitis

Table 2 Clinical classification of PH [2]

1.1.3 Exercise pulmonary hypertension

There has been a long way from first discussions of abnormal pulmonary hemodynamics to the recent definition of exercise PH (EPH). Although since 1960 the clinical relevance of exercise hemodynamics was discussed one decade later Hatano et al. were the first to define abnormal pulmonary hemodynamics with a mPAP exceeding 30 mmHg (Figure 2) [5,14]. In 2004 this definition of EPH with an exercise mPAP >30 mmHg was introduced in the ESC guidelines [15]. Following authors however criticized that mPAP alone is insufficient to describe EPH as the impact of aging on exercise hemodynamics and normal changes in cardiac output (CO) were not addressed adequately by a definition focusing on mPAP only [7]. Hence, the definition of EPH was removed from the 2009 and 2015 guidelines as a certain discrimination between physiological and pathological hemodynamic pattern during effort was not possible [6,16]. After more than one decade in 2022 EPH defined by mPAP/CO slope > 3 mmHg/L/min was reintroduced in the guidelines again [2].



3. **Normal pulmonary arterial pressure on effort**

Some forms of pulmonary hypertension are latent and become apparent only when there is an increase in blood flow. It is therefore important to know the response of the normal pulmonary circulation to effort.

Most of the measurements reported in the literature have been carried out in the *lying* position and show that the mean pulmonary arterial pressure rises proportionately less than the cardiac output.

For an output of 20 litres or more, the mean pulmonary arterial pressure does not normally exceed 30 mm Hg, and the capillary pressure remains below 20 mm Hg (8).

Figure 2 Extract of the recommendations of the First World Symposium on PH [5]

1.2 Pulmonary hypertension associated with lung diseases and/or hypoxia

Lung disease is the second most common reason for PH and associated with poor prognosis. Pulmonary diseases leading to PH include chronic obstructive pulmonary disease (COPD), emphysema, interstitial lung disease, combined pulmonary fibrosis and emphysema, hypoventilation syndromes, hypoxia without pulmonary disease and rarely obstructive sleep apnea, lymphangioleiomyomatosis, asthma, sarcoidosis, cystic fibrosis, Langerhans cell histiocytosis and hypersensitivity pneumonitis [2]. Out of the PH-lung group, COPD has the highest prevalence [17]. In the following we will further focus on COPD and PH (COPD-PH).

1.2.1 Classification of PH-lung in COPD

The classification of COPD-PH is challenging due to the discrimination between PH due to lung disease (group 3) and pulmonary arterial hypertension (PAH) (group 1) with pulmonary comorbidity. Some COPD patients may also have left heart diseases with consequently PAWP >15 mmHg and be classified into group 2 or chronic thromboembolic events and classified into group 4. Even if cardiovascular comorbidities and thromboembolic events are excluded, hemodynamics, ventilation and clinical features are necessary in order to categorize these patients correctly to group 1 vs. 3. Therefore, Humbert et al. provided an overview with characteristic diagnostic features that favors either group 1 or 3 (table 3) [2].

Diagnostic tool	**Group 1 (PAH)**	**Group 3 (PH associated with lung disease)**
Clinical presentation	▪ Young, female patients predominantly affected ▪ Clinical presentation depends on associated conditions and phenotype ▪ Oxygen requirement: uncommon, except for conditions with low DLCO or right-to-left shunting	▪ Mostly elderly patients, male predominance ▪ History and clinical findings suggestive of lung disease ▪ Smoking history ▪ Oxygen requirement for hypoxemia: common, often profound ▪ hypoxemia in severe PH
Chest radiography	RA/RV/PA dilatation Pruning of peripheral vessels	Signs of parenchymal lung disease
Pulmonary function tests and ABG	▪ Spirometry/PFT: Normal or mildly impaired ▪ DLCO: Normal or mild-to-moderately reduced ▪ Low DLCO in SSc-PAH, PVOD, and some IPAH phenotypes	▪ Spirometry/PFT: Impairment abnormal as determined by the underlying lung disease ▪ DLCO: Often very low (<45% predicted) ▪ PaO_2: Reduced

	▪ PaO_2: Normal or reduced ▪ $PaCO_2$: Reduced	▪ $PaCO_2$: anything
Echocardiography	▪ Signs of PH (increased sPAP, enlarged RA/RV) ▪ Congenital heart defects may be present	▪ Signs of PH (increased sPAP, enlarged RA/RV)
Lung scintigraphy	Normal or matched	Normal or matched
Chest CT	▪ Signs of PH or PVOD	▪ Signs of parenchymal lung disease ▪ Signs of PH
Cardiopulmonary exercise testing	▪ High VE/VCO_2 slope ▪ Low $PETCO_2$, decreasing during exercise ▪ No exercise ▪ oscillatory ventilation	▪ Mildly elevated VE/VCO_2 slope ▪ Normal $PETCO_2$, increasing during exercise
Right heart catheterization	Pre-capillary PH	Pre-capillary PH

Table 3 Characteristic diagnostic features of patients with PAH vs. PH-lung [2]

Despite this supportive table, the classification leaves some lack of clarity which COPD phenotype favors group 1 vs. 3. On the one hand, according to the guidelines pulmonary comorbidities in PAH may include signs of mild parenchymal lung disease and a DLCO <45 % predicted.

On the other hand, they state that the appearance of severe PH in PH-lung is independent of airflow limitation, but these patients usually reveal low diffusing capacity of lung for carbon monoxide (DLCO) <45 % as well and low arterial carbon dioxide partial pressure and hypoxemia, which are also typical features in PAH. In addition, mild obstruction may also be present in PAH and both group 1 and group 3 fulfill pre-capillary PH criteria. Finally, PAH studies usually have not utilized computer tomography or chest radiation in order to exclude patients with pulmonary diseases [2,18].

Therefore, a definition of relevant pulmonary disease that displays group 1 or 3 is lacking. Seeger et al. were the first group in 2013 to define relevant pulmonary obstructive disease as FEV1 < 60 % predicted in combination with morphological signs like emphysema [19].
At the 6th WSPH in Nice more detailed criteria to distinguish between PAH and PH-lung was introduced. According to this experts recommendation PH-lung for COPD patients should be favored if FEV1 is <60 % predicted, characteristic airways and/or parenchymal abnormalities in high-resolution computer tomography (CT) scan, patients have mild-moderate PH, additional PAH-risk factors are absent and cardiopulmonary exercise test (CPET) reveal features of exhausted ventilatory reserve, while PAH patients have FEV1 ≥ 60 % predicted, no or mild airway or parenchymal abnormalities, moderate to severe PH and features of exhausted circulatory reserve in CPET [20]. However, due to lack of evidence, these spirometry criteria were not included in the recent guidelines. More clinical studies are warranted to establish clinically relevant cut-offs.

1.2.2 Epidemiology

Mild to moderate PH is frequent in COPD patients with prevalence of a mPAP ≥25 mmHg in approximately 10% of the COPD patients [4,17]. With a global prevalence of COPD among people aged 30–79 years of 10,3% (391,9 million people) PH concerns a huge part of the world population [21]. Usually, these patients have moderate to severe airway obstruction and are classified to group 3. In patients with COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV the prevalence of PH is even higher. In up to 90% of patients with severe COPD a mild PH (mPAP >20 mmHg) is reported with the majority of them showing a mPAP between 25-35mmHg. Rarely, COPD patients have mPAP values > 35mmHg [2].

1.2.3 Clinical features and diagnostic tools

Invasive investigations in order to diagnose PH-lung in COPD should only be conducted during a stable phase of disease and under optimized therapy. Firstly, risk factors for PAH, CTEPH, left heart disease and other conditions leading to PH should be excluded and pulmonary disease should be confirmed. Patients with PH-lung often suffer from symptoms of the underlying lung disease overlapping with symptoms caused by PH. Dyspnea and stenocardia during exercise or even at rest, peripheral edema, exercise limitation and hypoxia are frequent in both conditions. [2].

Many diagnostic tools are recommended to collect information and confirm diagnosis. Electrocardiography (ECG) can be a simple tool and especially right axis deviation provides information of the probability of PH [22]. Concerning laboratory testing elevated levels of N-terminal-pro brain natriuretic peptide (NT-pro BNP) may suggest the existence of PH in COPD, although for moderate forms of PH, it has limited sensitivity and specificity [17]. Pulmonary function tests are recommended, albeit currently no spirometry thresholds are determined to define PH-lung in COPD. DLCO is considered to be low which corresponds to the obstructive changes [2,20]. The recommended non-invasive modality to confirm suspicion of PH is echocardiography. Besides maximal tricuspid regurgitation velocity (TRV) also right atrial area, the ratio of right to left ventricular size and the eccentricity index are recommended. Tricuspid annular plane systolic excursion (TAPSE) is an alternative measure to estimate right heart function [2,23]. However, especially in patients with COPD and emphysema echocardiography is often limited due to poor ultrasound conditions [24,25]. In addition, a main pulmonary artery enlargement, main pulmonary artery to ascending aorta diameter ratio > 1 and right heart hypertrophy assessed via CT may be further helpful to find PH in COPD [26,27]. Although CPET is of limited utility in the screening for PH-lung it might be a useful modality to assess hemodynamic and ventilatory limitations and may therefore help to identify the origin of exertional dyspnea during daily exercise [28].
According to the recent guidelines RHC should be performed in COPD patients to further phenotype them or when PAH or CTEPH is assumed. In addition, patients undergoing surgical procedures like lung transplantation or lunge volume reduction RHC is indicated [2]. In terms of rapid clinical worsening, progressively reduced exercise capacity, severe gas exchanges disorders or to estimate prognosis, a RHC may be considered [20].

1.2.4 Mechanisms of pulmonary vascular involvement in COPD

Flow limitation and loss of functional pulmonary parenchyma are characteristic changes in COPD, resulting in impaired daily physical capacity and poor prognosis. Destruction of pulmonary tissue, development of emphysema and resulting airway heterogeneities are the main pathological features in COPD [29,30]. PH may further complicate the course of COPD and affect survival, but the pathogenesis is still not fully understood [17,20,31].

As consequence to airway abnormalities hypoxic pulmonary vasoconstriction of non – or low-ventilated areas is the protection mechanism in order to maintain ventilation/perfusion (V/Q) match. In areas of chronic hypoxic pulmonary vasoconstriction, however, shear stress increases which triggers hypertrophy and proliferation of vascular smooth muscle cells. This leads to apoptosis, inflammatory response, and loss of pre-capillary pulmonary arteries as well as thickening of the media layer of the muscular arteries. Vascular remodeling is seen in patients with all stages of COPD and even smokers without hypoxemia and preserved lung function [32–34]. In addition, pulmonary vascular remodeling is caused by different molecular mechanisms in COPD-PH vs. PH in patients with idiopathic pulmonary fibrosis [35]. Moreover, emphysema results in further loss of small pulmonary arteries with the loss of terminal bronchi. In addition, dead space ventilation is increased and therefore air trapping and increased intrathoracic pressures can further contribute to elevated pulmonary arterial pressures. This is frequently seen during exercise [20,36]. Endothelial dysfunction of the pulmonary arteries in COPD was described since 1998 by several authors [37–39]. Consequently, vasoconstriction leads to increased pulmonary vascular resistance and contributes to PH. Besides pulmonary vessels, endothelial dysfunction was described of the systemic circulation of COPD patients as well [40]. This might be an explanation for arterial hypertension, left ventricular diastolic dysfunction, and associated cardiovascular events in COPD, also contributing to PH [38,41]. A possible explanation for the endothelial dysfunction might be chronic inflammation, which is a frequent finding in COPD [42]. Inflammatory cytokines affect endothelial and smooth muscle cells of the pulmonary arteries, which may cause pulmonary vascular disease [38,39,43]. Tobacco smoking can lead to pulmonary vascular remodeling prior to the development of COPD [38]. Smoking can induce endothelial and epithelial damage resulting in pulmonary structural and vascular changes. These changes may impact pulmonary pressures, as former described [44–46]. Moreover, inflammatory processes in smokers have been discussed to induce pulmonary arterial remodeling [47]. Finally, some authors assume a genetic

predisposition for pulmonary vascular involvement in COPD subjects [48]. For example, a somatic polymorphism of the serotonin (5-HT) transporter gene was shown to be associated with the severity of PH in hypoxic COPD patients [49]. In addition, Nagaraj et al. recently found, that the expression of p22phox, a regulatory subunit of Nox which is a key disease-related factor in vascular diseases was correlated to mPAP and DLCO, suggesting a role of this gene in V/Q mismatch and pulmonary arterial remodeling [50]. All these introduced mechanisms affect pulmonary circulation and therefore may contribute to pulmonary hypertension.

1.2.5 Therapy

In the setting of mild-to moderate PH, optimizing the COPD treatment has first priority. This includes anti-obstructive medication and whenever indicated diuretics, supplementary oxygen, non-invasive ventilation, rehabilitation programs, exacerbation prophylaxis, eg. Vaccinations and as ultima ratio to consider lung transplantation [2]. However, data whether this optimized therapy contributes to an improvement in pulmonary hemodynamics are conflicting, as some authors showed decrease of PAP and PVR under long-term oxygen, others found no change both under long-term oxygen therapy as well as on non-invasive ventilation [51–53]. There is agreement anyway, that patients with severe PH-lung should be referred to an expert center for an individual decision making.

According to the 2022 ERS/ESC guidelines there is no recommendation for the use of targeted PAH therapy in COPD-PH patients due to conflicting literature and lack of evidence. Severe adverse events on circulation, gas exchange, exercise capacity and consequently outcome are dreaded complications due to inhibition of hypoxic vasoconstriction by vasodilator therapy and therefore worsening V/Q mismatch. In a placebo-controlled trial by Stolz et al. COPD patients with mild-moderate PH did not improve exercise capacity by means of 6MWT but deteriorated with arterial oxygen pressure, alveolar-arterial gradient and quality of life under endothelin receptor antagonist therapy [54]. Further studies brought similar results or showed no effect on exercise, gas exchange and quality of life [55–57]. Of note, all these patients had severe airway obstruction with only mild or even without pulmonary hypertension suggesting that this might not be the optimal collective to benefit from PAH therapy.

In contrast studies including COPD patients with moderate - severe PH revealed an improvement of hemodynamics. In a study conducted by Vitulo et al. significant improvement in PVR and quality of life after 16 weeks of phosphodiesterase 5 inhibitor (PDE5i) therapy were detected [58]. In addition, approximately one third of COPD patients with severe PH from registry data improved in World Health Organization Functional class (WHO-FC), PVR, 6MWT and transplant-free survival when treated with PDE5i [33,59]. Further studies found in severe COPD-PH improvement in six-minute-walk test (6MWT), mPAP, cardiac index and survival under targeted therapy [60–62].

The use of inhaled Treprostinil for patients with ILD-PH was approved in 2021 by the US Food and Drug Administration (FDA) after data from the INCREASE study were published that demonstrated a significant improvement in exercise capacity from baseline at 16 weeks compared to placebo (95% CI: 16.9–45.4 m; $p < 0.001$) [63]. Due to the limited local effect of an inhalative targeted therapy this might be an interesting new approach to treat severe COPD-PH patients effectively and to avoid circulatory side effects at the same time. For COPD patients however, excepting one study of very low power but positive results, no data exists of treating COPD-PH patients with inhaled prostacyclin analogue [64].

In summary, targeted PAH-therapy might be a treatment option for a carefully selected subgroup of COPD-PH.

1.2.6 Definition of severe and non-severe PH-lung

Based on the growing evidence that a subset of patients with severe PH-lung may profit from targeted PAH therapy, much effort has been directed towards defining what is severe PH-lung. At the Cologne Consensus Conference in 2010 severe PH-lung was defined by two of three present criteria [33,65]:

- mPAP >35 mmHg
- mPAP ≥25 mmHg and cardiac index (CI) < 2,0 ml/min/m²
- PVR > 6 WU

In the 2015 ESC/ERS Guidelines for the diagnosis and treatment of PH PVR was abandoned and CI was raised:

- mPAP >35 mmHg or
- mPAP ≥25 mmHg and cardiac index (CI) < 2,5 ml/min/m²

However, the prognostic impact of significantly increased PVR was shown by several authors in the past decade and therefore reintroduced into the recent guidelines [33,59,66,67]. The threshold for the definition of severe PH-lung resembles the suggested cut-off in 2010:

- PVR > 5 WU

Of note, the determination of only PVR is currently required to define severe PH but nearly all existing data are based on the former definition [2].

1.3 Pulmonary vascular phenotype

Within the PVD cohort, some authors support the existence of a unique cluster of those COPD-PH subjects who have mild-moderate airway limitation but moderate to severe PH, the so-called pulmonary vascular phenotype (PVP). This hypothesis was supported by differences in the specific features of these patients regarding lung function, exercise testing, response to targeted PAH treatment, disease progression or prognosis compared to mild-moderate COPD PH that will be introduced in this chapter [68].

The pulmonary circulation is often abnormal in COPD patients, however only a few subjects develop severe PH. Approximately 1-5% of all cases of COPD have severely elevated mPAP values of > 35mmHg and massive dyspnea despite only mild to moderate airflow limitation. Additionally, obstruction patterns are correlated to severity of PH [17,69]. Almost two decades ago in 2005 Thabut et al. performed a cluster analysis in advanced COPD patients and identified different clinical profiles in one cluster of patients characterized by moderate obstruction and moderate-to-severe pulmonary hypertension as well as seriously hypoxemia compared to the rest [70]. Chaouat et al found in the same year a subgroup of COPD patients with severely elevated mPAP and only mild - moderate airway obstruction but pronounced hypoxemia, hypocapnia, very low DLCO, exertional dyspnea and reduced survival compared to COPD patients without severe PH [69]. In addition, Boerrigter et al. showed that severe COPD-PH patients were limited due to the circulation in CPET and not due to both ventilation and circulation as patients with non-severe COPD-PH [71]. These authors support the existence of a PVP by different clinical profiles.

Any elevation of pulmonary arterial pressure negatively affects hospitalization and prognosis [17,72–74]. However, severe COPD-PH patients have an impaired outcome compared to COPD patients with mild-moderate PH and even a worse prognosis compared to patients with idiopathic PAH (IPAH) [33,75,76]. Moreover, mild-to moderate COPD patients without PH do not inevitably reveal signs of cor pulmonale, but may have preserved right heart function [77]. Patients with severe COPD-PH however, show progressive RV failure similar to IPAH patients, which is associated with poor prognosis [69,78–80]. PAP and dilatated pulmonary arteries were identified as predictors of exacerbations and PVR was associated with disease progression in COPD [26,68,81]. The fact, that severe COPD-PH patients have progressive RV failure, show

progressive primary disease and worse prognosis than non-severe COPD-PH or patients with normal PAP and that prognosis is more comparable to IPAH patients than to non-severe COPD-PH subjects further advocates a PVP.

The pathogenesis of COPD-PH was described above; however, mechanisms are not fully understood. It is supposed that the development of PVD and in particular PVP goes beyond loss of pulmonary vessels and chronic hypoxemia. The driving force of PVP is more suspected on a pulmonary vascular remodeling pathway, similar but not identical to PAH [68,82]. This theory is supported by concomitant histological findings by Carlsen et al who showed that severe COPD-PH patients show characteristic morphologic lesions similar to IPAH and that the extent of pulmonary vascular lesions in COPD patients are associated with the severity of PH [83]. In contrast to moderate PH pulmonary vascular remodeling seems to differ in severe PH-COPD, who predominantly show remodeling of the micro vessels and have lower capillary density [84]. In addition, COPD patients with PH (mPAP $\geq$ 25mmHg) have significantly more intima thickening of small vessels than non-PH COPD subjects [35]. We recently confirmed these findings when comparing pulmonary arteries, parenchyma, and airways of mainly severe COPD-PH lungs vs. non-severe COPD-PH lungs and therefore favoring a PVP in COPD-PH [85].

Figure 3 shows typical histological findings of pulmonary arteries of explanted lungs of healthy donors, COPD without PH, COPD-PH and IPAH patients. Of note, compared to healthy donors and COPD lungs without PH, those from COPD-PH and IPAH show intima hypertrophy, intima fibrosis and media hypertrophy, albeit IPAH had by far the greatest degree of pulmonary vascular remodeling.

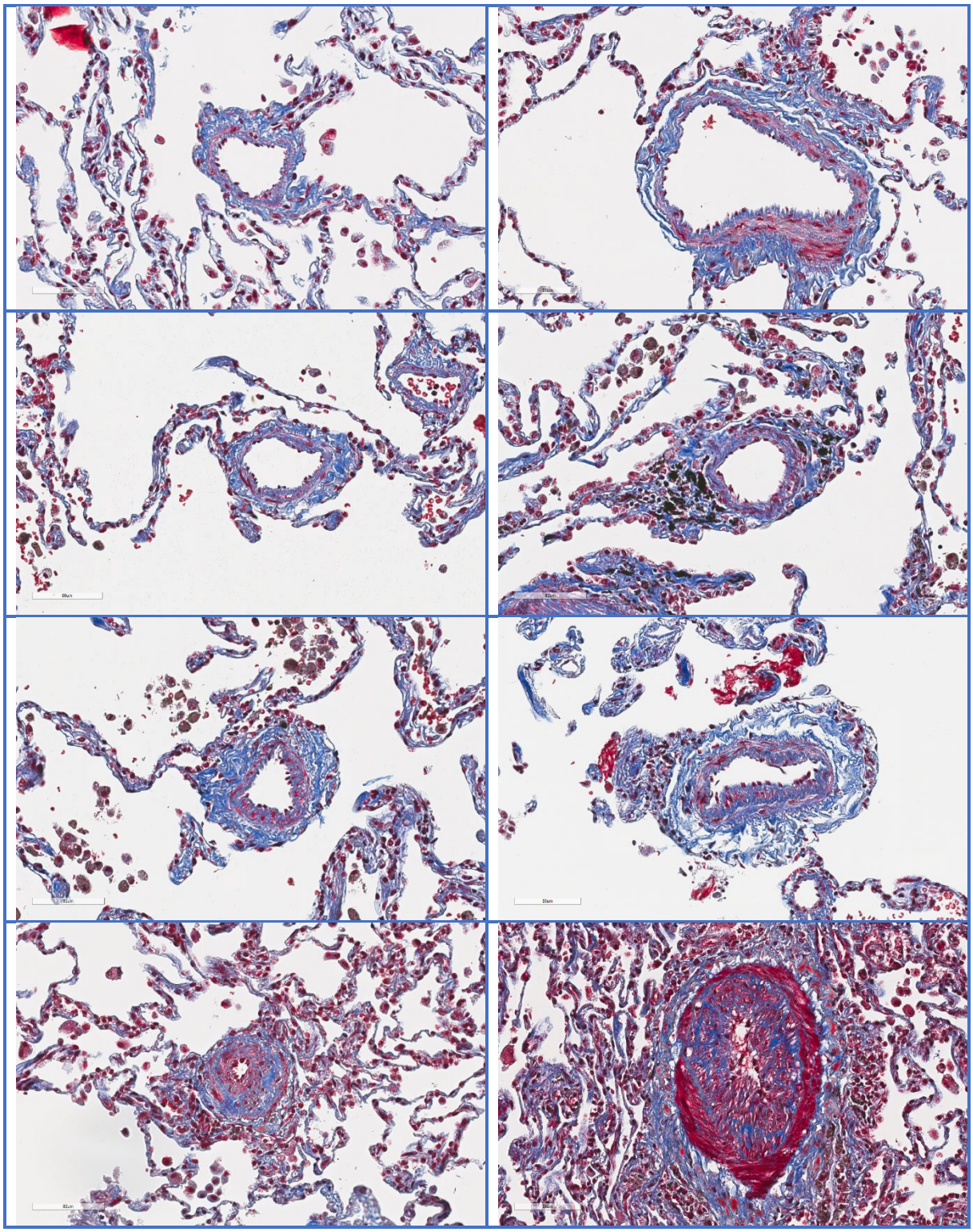


Figure 3 Representative images of pulmonary arteries
Healthy donors (a), COPD (b), COPD-PH (c) and IPAH patients (d). Masson's trichrome staining was performed on 3 µm FFPE-tissue of transplanted patients and downsized donor lungs. Scale bar: 80 µm. Images with friendly permission from Katharina Jandl, PhD, Ludwig-Boltzmann Institute of lung vascular research.

As previously mentioned, several authors described a significantly improvement of pulmonary hemodynamics (CI, mPAP, PVR), exercise capacity (6MGT), PH symptoms (WHO-FC),

quality of life and survival on targeted PAH therapy [33,58–62]. These benefits were only detected in severe COPD-PH patients while non-severe COPD-PH subjects revealed no change in hemodynamics and exercise tolerance but even worsening of oxygen partial pressure, alveolar-arterial oxygen gradient and Quality of life [54–57]. Therefore, it seems that only a carefully selected collective of COPD-PH patients may profit from medication approved for PAH.

Based on all these findings several authors suspect the existence a PVP in this subset of patients in whom PVD is predominant including severe precapillary PH, moderate obstruction, no or mild hypercapnia, DLCO <45 % predicted and circulatory limitation in CPET [68]. A proper discrimination of PVP, PAH and COPD patients with emphysema should be aspired. Particularly the latter group may show signs of severe PH, severely reduced DLCO, exertional dyspnea, limited exercise tolerance and poor outcome, which complicates the distinction of PVP and PH-lung due to emphysema [86].

Table 4 summarizes the available knowledge of discrimination of different disease phenotypes, that were introduced in this chapter. Further studies of larger sample size are warranted to ensure more evidence of the suggested parameters to confirm a PVP in COPD-PH.

	PH-lung with emphysema	Mild-moderate COPD-PH	PVP	PAH
$PaCO_2$	~	~/↑	~/↓	~/↓
FVC/TLC/RV	↑	~/↑	~	~
mPAP PVR	↑(↑) ↑	↑ ↑	↑↑↑ ↑↑	↑↑↑ ↑↑
Histology: Airway abnormalities	↑↑↑	↑↑	↑	-
Parenchymal remodeling	↑↑↑	↑↑	↑	-
Pulmonary arteries	Intima proliferation↑ Media hyperplasia↑	Intima proliferation↑ Media hyperplasia↑	Intima proliferation↑↑ Media hyperplasia↑↑	Intima proliferation↑↑↑ Media hyperplasia↑↑↑ Plexiform lesions
Pathological CT findings	Airway changes↑ Parenchymal changes ↑↑	Airway changes↑↑ Parenchymal changes ↑	Airway changes↑ Parenchymal changes ↑	~ ~
CPET limitation	Ventilatory > cardiovascular	Ventilatory > cardiovascular	Cardiovascular > ventilatory	cardiovascular
Response to PAH therapy	↓	↓	↑	↑↑

Table 4 Discrimination of different pulmonary hypertension phenotypes
Explanation: -= no influence, ~ = rather no change, ↓=rather decrease, ↑=rather increase, 1 arrow= mild, 2 arrows=moderate, 3 arrows= severe

1.4 Early pulmonary vascular disease

Beside significant PH, there is data suggesting that even mildly elevated mPAP (defined as <25 mmHg) is associated with worse outcome and hospitalization in COPD-PH [17,72–74]. Regardless of normal or mildly elevated resting pulmonary arterial pressures these patients may suffer from exertional dyspnea during exercise, that is not only explainable by ventilatory limitation. An abnormal hemodynamic response to exercise is therefore assumed in these patients, which could remarkably contribute to their exercise limitation and may explain exertional dyspnea [81,87–89]. In recent years, much effort has been directed towards improving our understanding of exercise pulmonary hemodynamics, finding clinically relevant variables, and defining EPH. Based on several studies pressure/CO-slopes were identified as most robust parameters in order to characterize abnormal pulmonary hemodynamics during exercise and was therefore reintroduced in the current guidelines [2,87,90–92].

1.5 Hypothesis and aims

Our understanding of pulmonary hemodynamics during exercise improved within the past few years, however, data investigating the characteristic of changes in pulmonary hemodynamics at exercise in COPD patients as well as the clinical relevance of these changes are still very limited.

In the current study, our aim was to investigate pulmonary hemodynamics and RV function during exercise in patients with COPD and normal or mildly elevated resting mPAP and to compare them to age- and sex-matched controls. We hypothesized that even in COPD patients without significant PH at rest, abnormal pulmonary hemodynamics during exercise may affect exercise capacity.

2 Material and Methods

2.1 Study design and patients

We evaluated all consecutive COPD patients from our local database, the **GRA**z **P**ulmonary **H**ypertension **I**n **C**OPD (**GRAPHIC**) registry who underwent right heart catheterization (RHC) for clinical suspected PH between 2005 and 2018. The GRAPHIC registry includes COPD patients who referred to our outpatient pulmonary clinic were carefully clinically evaluated with complete dataset [31]. When investigation was performed, patients with normal pulmonary hemodynamics at RHC (resting mPAP <25 mmHg) underwent exercise-RHC to receive additive information with regard to mechanisms of disproportionate dyspnea, reduced exercise capacity and to detect early PVD [6,15,16]. If more than one exercise RHC was performed, we included only the first investigation.

2.1.1 Inclusion criteria

Patients with following criteria were included in our analysis:

- COPD (GOLD I-IV) with unexplained dyspnea and/or signs PH
- mPAP <25mmHg and PAWP ≤ 15mmHg
- exercise right heart catheterization performed

The diagnosis of COPD and the severity of airflow limitation were established according to the GOLD recommendations by two independent respiratory physicians [29].

2.1.2 Exclusion criteria

Patients with following criteria were excluded from our analysis:

- resting mPAP ≥ 25 mmHg or PAWP > 15mmHg
- missing important resting or exercise hemodynamic data (mPAP, PAWP, RAP, PVR, CO, CI)

2.1.3 Control group

Controls were age- and sex-matched to the COPD.

The individuals for the control group were selected according to the following criteria:

- Patients who presented at our outpatient pulmonary clinic between 2005 and 2018 because of unexplained dyspnea and/or of clinical suspicion of PH
- Exclusion of chronic lung disease, in particular neither obstruction nor restriction (FEV1/FVC > 70 % and TLC > 80 %)
- Maintained exercise capacity with a peak oxygen uptake (VO2) ≥ 80 % predicted
- Resting mPAP < 25 mmHg and resting PAWP ≤ 15 mmHg at invasive RHC

2.2 Clinical investigations

In the context of their clinical work-up routine focusing on signs and symptoms of pulmonary vascular disease, patients underwent laboratory testing, pulmonary function testing, blood-gas analysis, electrocardiography, transthoracic echocardiography, 6MWT, cardiopulmonary exercise testing (CPET), and invasive resting and exercise RHC. Control patients underwent the same diagnostic approaches as the COPD patients.

2.2.1 Clinical parameters

Standard characteristic parameters were assessed in all subjects including body weight, height, body mass index (by body weight in kilogram divided by squared height in meters), medical intake, longterm oxygen therapy, comorbidities, smoking status, pack years (py), WHO-FC and for COPD patients GOLD stage. The WHO-FC describes the severity of symptoms of a patient with PH, ranging from mild class I to the most severe class IV and was adapted based on the New York Heart Association classification for assessing patients with PAH (Table 5) [93]. This classification is widely used for risk evaluation, treatment decisions, disease progression and prognosis in PAH [2,94].

WHO-FC	Definition
Class: I	No exercise limitation, daily activity does not cause disproportional dyspnea, fatigue, chest pain, or presyncope
Class: II	Little exercise limitation, ordinary daily activity causes disproportional dyspnea, fatigue, chest pain, or presyncope
Class: III	Severe exercise limitation, less than ordinary physical activity causes disproportional dyspnea, fatigue, chest pain, or presyncope
Class: IV	Dyspnea and fatigue even at rest, any physical activity causes symptoms and discomfort.

Table 5 World Health Organization functional classification of PH patients [95]

GOLD stages allow a grading of COPD patients due to their disease progression (Table 6).

GOLD grade	Severity	FEV1/FVC < 70% predicted and
GOLD I	Mild	FEV1 ≥ 80 %
GOLD II	Moderate	FEV1 50-79%
GOLD III	Severe	FEV1 30-49%
GOLD IV	Very severe	FEV1 <30 %

Table 6 GOLD grades and severity of airflow limitation in patients with COPD [29]

Frequency of exacerbations and hospitalization and symptoms evaluated by COPD Assessment Test (CAT) or modified Medical Research Council (mMRC) dyspnea scale are assessed to guide treatment decision (Table 7).

≥2 moderate exacerbations or ≥1 leading to hospitalization	E	
<2 moderate exacerbations and no hospitalization per year	A	B
Symptoms	mMRC 0-1 CAT < 10	mMRC ≥ 2 CAT ≥ 10

Table 7 GOLD ABE Assessment Tool

2.2.2 Laboratory testing

Routinely conducted laboratory testing included complete blood count (e.g. hemoglobin (Hb), white blood counts, platelets), differential blood count, coagulation parameters, renal function parameters (creatinine, uric acid, glomerular filtration rate), liver function parameters (liver enzyme profile, bilirubin, albumin) markers of cardiac function (NT-proBNP), triglycerides, blood cholesterol level, c-reactive protein and glucose.

2.2.3 Pulmonary function testing

Pulmonary function testing is a required assessment in order to discriminate PH subtypes [2]. Investigations including spirometry, bodyplethysmography and measurement of carbon monoxide diffusion capacity (DLCO) were undertaken under standard conditions by experienced biomedical analytical technical personal. Prior to the measurement baseline data including age, sex, body weight, body height, body mass index and smoking history were collected and saved. For spirometry (Masterlab Body Pro Jaeger, Höchberg, Germany) patients had to sit in an upright position and wear a nose clip. Patients were instructed to maximal expire and then inspire as fast as possible. With this maneuver, forced vital capacity (FVC) can be measured. Afterwards, they had to inspire as much air as possible and then to exhale as much and as fast as possible in order to determine forced expiratory volume in 1 second (FEV1). Investigations were repeated until three acceptable measurements were performed. Tiffenau-Index was calculated by FEV1/FVC. For bodyplethysmography, patients were seated in the bodyplethysmography chamber with nose clip and after a few resting breathings, patients had to exhale against a flow blocker. Vital capacity (VC), total lung capacity (TLC) and Residual volume (RV) were determined from bodyplethysmography. For DLCO measurement, we used the Master-Screen-PFT Jaeger device (Höchberg, Germany). Patients were pleased to inhale a harmless amount of carbon monoxide gas. After a few calm breaths, they were instructed to exhale deeply and then to take a deep breath and hold breath for ten seconds. After exhalation, the investigation is terminated. Thereby, DLCOc VA (corrected for hemoglobin- and alveolar space volume) and DLCOc SB (single breathe, corrected for hemoglobin) can be determined. The percent of predicted was calculated, based on absolute values for each variable.

2.2.4 Blood-gas analysis

For blood gas analysis (BGA), we used ABL-800-FLEX blood gas analyzer (Drott, Austria) (Figure 4a). Blood samples were drawn from arterialized blood from a hyperemic ear lobe using Finalgon ® salve. Values assessed by BGA included concentration of hydrogen protons (PH), arterial partial pressure of oxygen (PaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$), base excess (BE), arterial oxygen saturation (SaO_2), oxygen uptake (VO_2) and arterial to mixed venous oxygen difference ($AVDO_2$) (Figure 4b). In addition, during RHC blood was taken from the central venous vessel and the pulmonary artery. Thereby mixed venous saturation (SvO_2) and central venous saturation ($ScvO_2$) were measured in order to provide information about intracardial shunts.

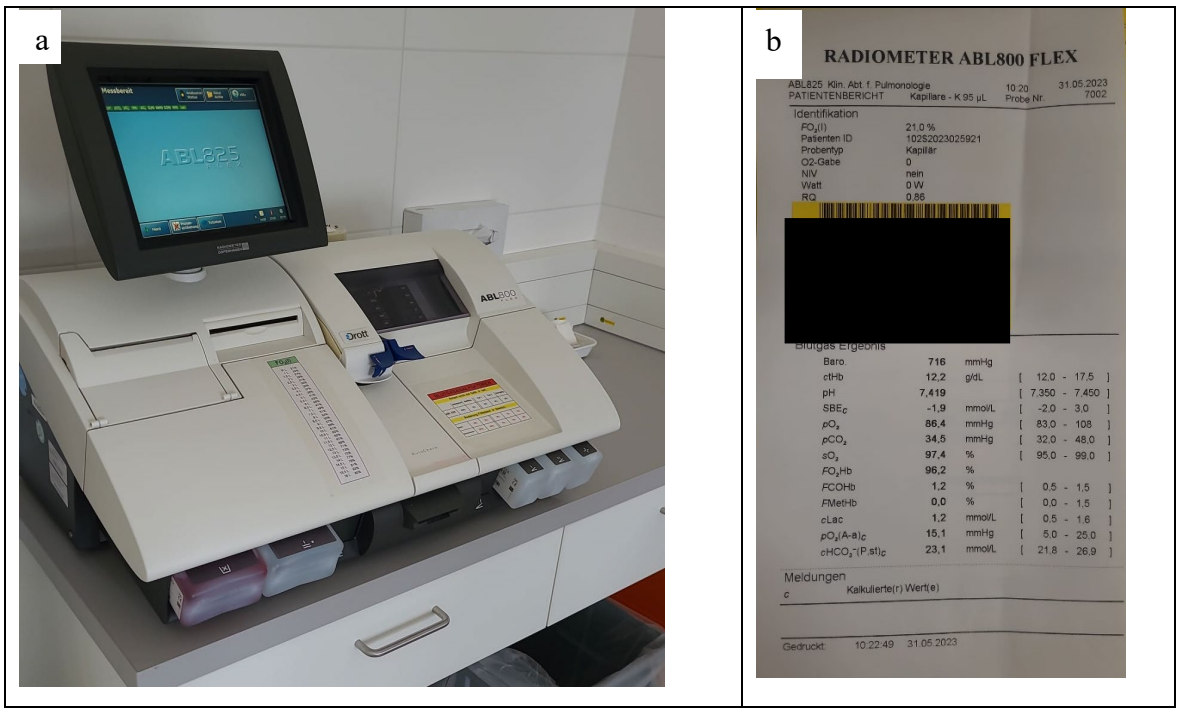


Figure 4 Blood gas analyses device ABL 800 FLEX (a) and BGA example (b)

2.2.5 Electrocardiography

Resting 12-lead electrocardiography (ECG) written with 50mm/s was performed in all subjects to provide fast, easy, and non-invasive information about possible right heart shear signs. MAC 3500 device by GE Healthcare was used (Figure 5). According to the recommendations signs for PH including P pulmonale, right axis or sagittal axis deviation, RV hypertrophy, complete or incomplete right bundle branch block, RV strain defined as ST depression and/or T-wave

inversion in the right precordial and inferior leads and prolonged QTc interval were focused in particular [2].

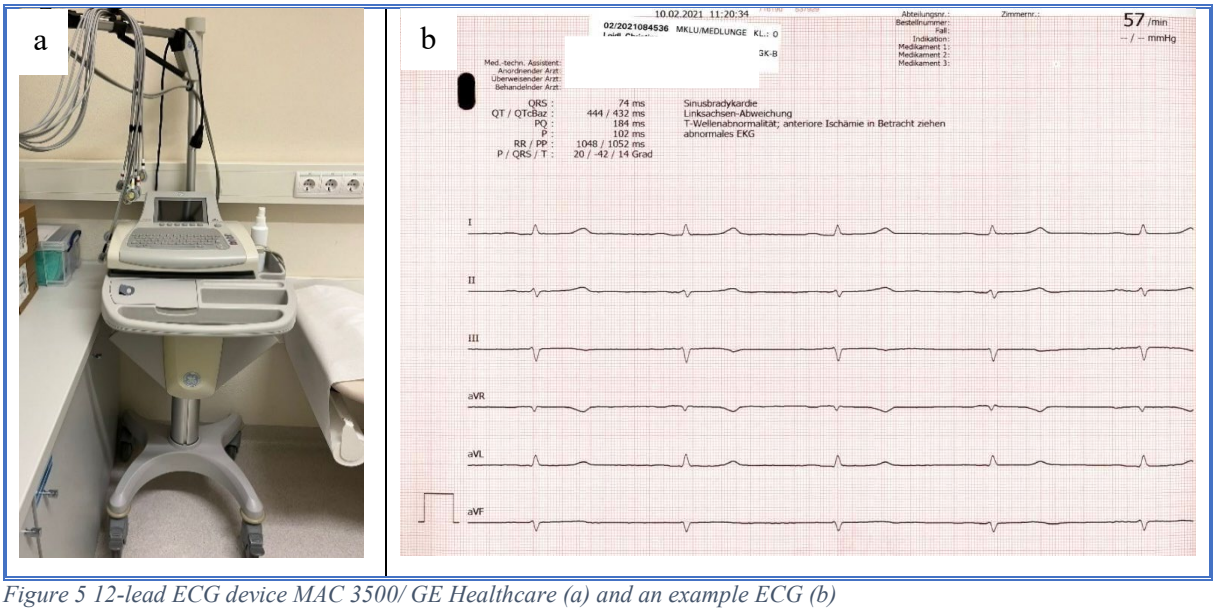


Figure 5 12-lead ECG device MAC 3500/ GE Healthcare (a) and an example ECG (b)

2.2.6 Transthoracic echocardiography

Transthoracic echocardiography is the main recommended screening device for PH, although echocardiography is not able to replace RHC, which is the gold standard [2]. Echocardiography was performed with Vivid Five GE healthcare Vingmed Ultrasound® device with a 3.5 mHz phased transducer from 2005 to 2012 and a Vivid E9 Ultrasound® device by GE healthcare using a 4.5 mHz ultrasound probe from then on (Figure 6a). Investigation and standard views were performed according to the guidelines [96].

Whenever tricuspid regurgitation (Figure 6b) existed, continues wave (CW) Doppler sonography in order to determine tricuspid regurgitation velocity (TRV) during systole was assessed (Figure 6c). Systolic (s) PAP was calculated by simplified Bernoulli equation (gradient pressure = $4*TRV^2$) plus an estimation of right atrial pressure (RAP) [97]. Right atrial pressure RAP was estimated by assessing the diameter and collapse grade of the inferior vena cava (VCI) (Figure 6d) [2].

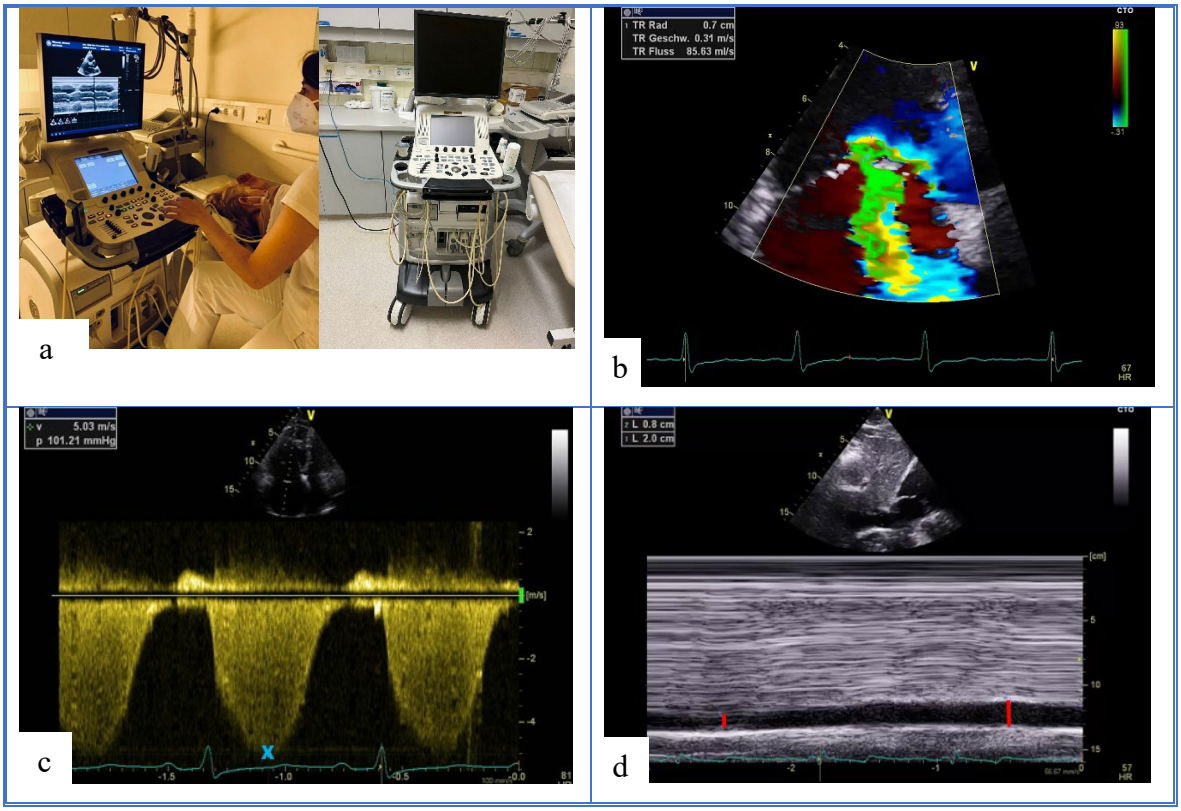


Figure 6 Vivid E9 Ultrasound device, GE healthcare (a), determination of sPAP (b-d)

As the estimation of sPAP is highly dependent on inter observer reliability and patient factors, echocardiography is currently only recommended for screening for PH but still does not replace invasive RHC to diagnose PH [98]. Further echocardiographic signs arguing for pulmonary hypertension, according to the current guidelines, that were eventually recorded, are listed in table 9.

Enlarged RV with RV/LV ratio >1	D-sign with decreased eccentricity index
Acceleration Time <105ms in RV outflow tract and notching of mid systolic flow signal (CW Doppler)	Peak systolic velocity (s') of tricuspid annular plane <9,5 cm/s (Tissue Doppler)
TAPSE <18 mm (M-Mode)	Fractional area change <35% (B-Mode)
Right atrial area > 18cm²	Peak TRV > 2,8 m/s
Pericardial effusion signs	Distended VCI with diminished inspiratory collapse (B-and M-Mode)

Table 8 Echocardiographic parameters in the assessment of PH

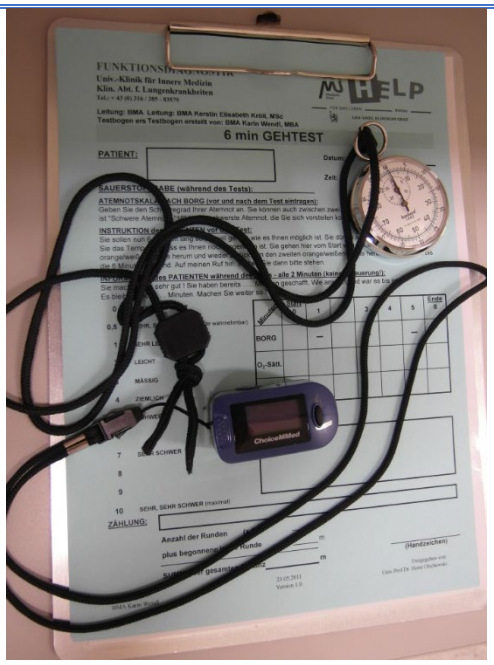
2.2.7 Assessment of exercise capacity

In order to assess individual exercise capacity, we performed 6MWT and CPET. Both investigations are used to guide treatment decisions in PVD and are markers of quality of life and prognosis in PH patients [2,99,100].

2.2.7.1 6-Minute walk test

6MWT was performed according to recent ATS guidelines under standardized conditions in our pulmonary outpatient clinic (Figure 7) [101]. Therefore, patients were instructed to walk 6 minutes as fast as possible without causing inconvenience. Cumulative walking distance was documented. BORG scale, heart rate and oxygen saturation (by fingertip pulse oximeter MD300D/HABEL Medizintechnik) were noted at baseline and every 2 minutes until the last measurement. BORG categorical ratio reflects the subjective level of dyspnea ranging from 0 (no exertion or dyspnea) to 10 (maximum exertion or dyspnea).

a



b

Figure 7 Utensils and protocol used for 6MWT and walking distance

2.2.7.2 Cardiopulmonary exercise testing

CPET is the gold standard for the determination of exercise capacity and helps to discriminate between exercise limitation due to cardiovascular, respiratory, muscular wasting or conditioning reasons. For CPET an ergoline ergoselect 1200/ Bergmann Medizintechnik GmbH® ergometer device was used. Contraindications for CPET were based on previously published guidelines [102].

Patients were seated in semi-reclined position, wearing a nose clip and breathing into a mouth piece with a turbine pneumotachograph recording gas volumes. Non-invasive blood pressure, oxygen saturation and ECG was measured to monitor the subjects. Initially, a two minutes resting phase was performed. Afterwards a stepwise increase of work load (25 watt) every 2 minutes was performed, maintaining 55 to 65 revolutions per minute. BGA was taken at rest, at peak exercise, three minutes - and eight minutes after exercise termination. Possible reasons for exercise termination were documented. Subjective reasons for exercise termination were maximal exertion and limited due to symptoms (angina pectoris, dyspnea, muscular weakness, others). Objective reasons for exercise termination included ischemia signs in ECG, complex dysrhythmia, second- or third-degree heart block, decline in systolic blood pressure > 20 mmHg, severe systolic hypertension > 250 mmHg or severe diastolic hypertension > 120 mmHg, desaturation ≤ 80%, sudden pallor or shock signs, unconsciousness and signs of respiratory failure.

Parameters that were measured and calculated included tidal volume (VT), respiratory rate (RR), end-tidal PO2 ($PETO_2$), end-tidal PCO2 ($PETCO_2$), blood pressure, heart rate, minute ventilation (VE), oxygen uptake (VO_2), carbon dioxide output, oxygen pulse (VO2/HR), dead space volume, ratio of physiologic dead space to tidal volume, peak oxygen uptake ($peakVO_2$), respiratory equivalents for O2 and CO2, anaerobic threshold, respiratory exchange ratio (RER) and metabolic equivalent. $PeakVO_2$ was the main variable, of which the percent of predicted was calculated.

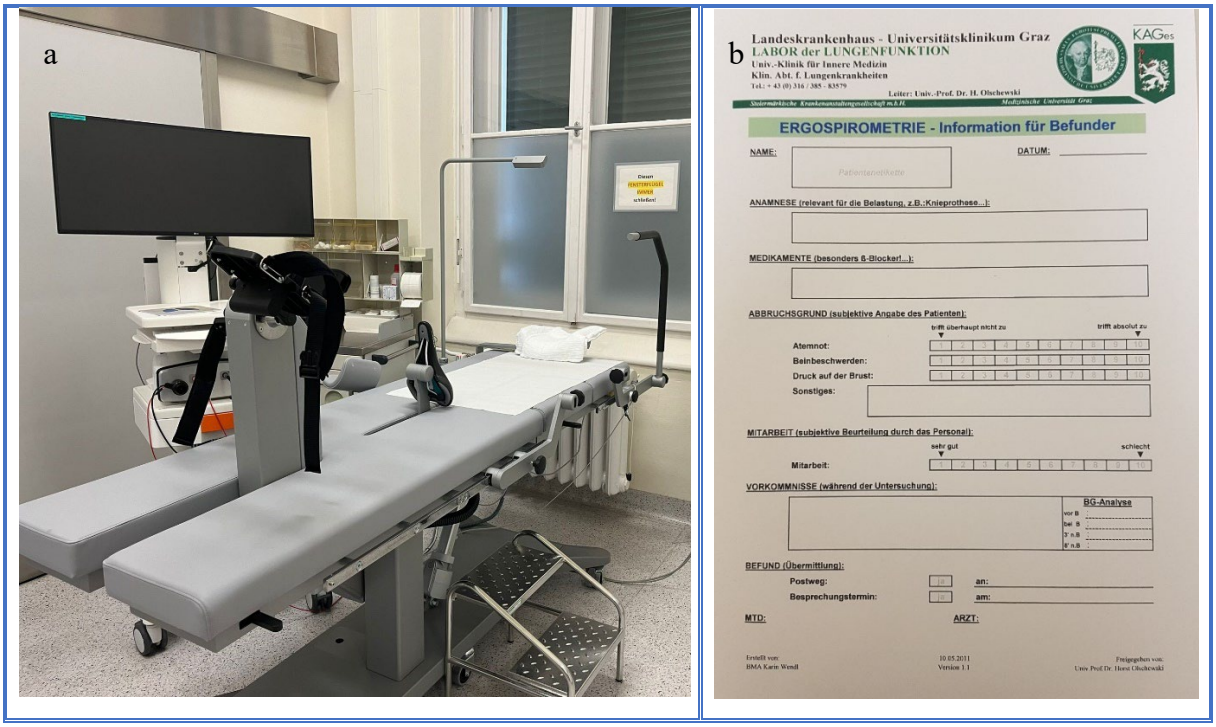


Figure 8 Ergometer device (Ergoline ergoselect 1200) (a) and protocol (b)

2.2.8 Assessment of resting and exercise hemodynamics

Invasive resting and exercise RHC is the gold standard diagnostic tool in order to diagnose and classify PH [2]. Patients and controls underwent routine resting RHC in a supine position using a Swan-Ganz catheter as previously described [103]. The catheter was inserted percutaneously into the right (preferred) or left jugular vein under local anesthesia. The mid-thoracic level was used as zero reference level as recommended [104,105]. Exercise RHC was performed in supine position on a cycle-ergometer with incremental increase of 25 watt work load every two minutes until symptom limited exercise termination (Figure 9).

SPAP, mPAP, diastolic pulmonary arterial pressure (dPAP), PAWP, RAP and via thermodilution determined CO were measured at each exercise level. Pressures were averaged over at least three respiratory cycles. For thermodilution 10ml of approximately 12°Celcius cold 0.9% sodium chloride solution was injected. We calculated total pulmonary resistance (TPR) as mPAP/CO, transpulmonary pressure gradient (TPG) as mPAP-PAWP and PVR as TPG/CO. Pressure/flow slopes were determined as differences between peak exercise and resting of mPAP/PAWP/RAP/TPG, respectively and the differences between peak exercise and resting CO [92,106].

Figure 9 Cycle ergometer during exercise RHC (a) and Svan-Ganz catheter lines (b)

Further secondary calculated values included cardiac index (CI), pulmonary vascular resistance index and systemic vascular resistance and index. Pulmonary vascular compliance (PVC) was estimated by stroke volume (SV)/(sPAP–dPAP), pulmonary artery (PA) stiffness index by 1/PVC per body surface area and right ventricular output reserve (RVOR) = $CI_{max\text{-}rest}/CI_{rest}$. Blood gas analysis was performed at baseline and at peak exercise.

2.3 Statistical analysis

Normally distributed variables are represented as mean ± standard deviation and continuous data as median and interquartile range (IQR). Categorical data are shown as absolute and relative numbers. Groups comparisons were performed with chi-square tests. Mann-Whitney-U-test was performed for group comparisons of continuous variables and Kruskal Wallis test for non-parametric data. Correlation analysis were analyzed with Spearman rank (r_{rho}, r_{ρ}) correlation coefficient. Survival data were obtained from the Federal Institute for Statistics Austria (Statistik Austria, Guglgasse 13, 1110 Vienna, Austria). Missing data were taken from insurance data. Hospitalization was identified by using local data information system (openmedocs) and ELGA, a digital health data collection platform in Austria.

Survival, defined by time from RHC to death, and cumulative endpoint of either disease-related hospitalization or death and was shown graphically by Kaplan Meier curves. We determined significance level with p-value of <0.05. Statistical analysis was performed with IBM SPSS Statistics software (26, Chicago (IL), USA: SPSS Inc., an IBM Company).

2.4 Ethical issues and data protecting

The study was approved by the local Ethics Committee of the Medical University of Graz (EK 32-352 ex 19-20). The protocol conformed to the Declaration of Helsinki. We saved patient related data on a firewall-protected and password-saved server of the Medical University of Graz. All data were saved anonymously in Microsoft Office Excel 2016 program and only authorized personal had access to the server.

3 Results

3.1 Patient characteristics

In our database, 213 patients with COPD who underwent invasive RHC between 2005 and 2018 were identified. As our aim was to assess the influence of physical activity in COPD patients with only mild PH or without manifest PH, all patients with missing CPET (N= 71) were excluded from our retrospective analysis. Furthermore, we aimed to investigate exercise pulmonary hemodynamics. Therefore, 115 patients who only underwent resting RHC without exercise RHC were also not considered for the analysis of the current study. Out of the remaining 27 subjects with resting and additional symptom-limited exercise RHC, one patient was excluded because mPAP at rest was above 25 mmHg (with 29 mmHg). In summary, a total of 26 COPD patients were included in our retrospective analysis. We age- and sex- matched them to controls without chronic lung disease and normal cardiopulmonary exercise performance, defined by peakVO_2 ≥ 80% predicted. Figure 10 shows the procedure of our patient selection.

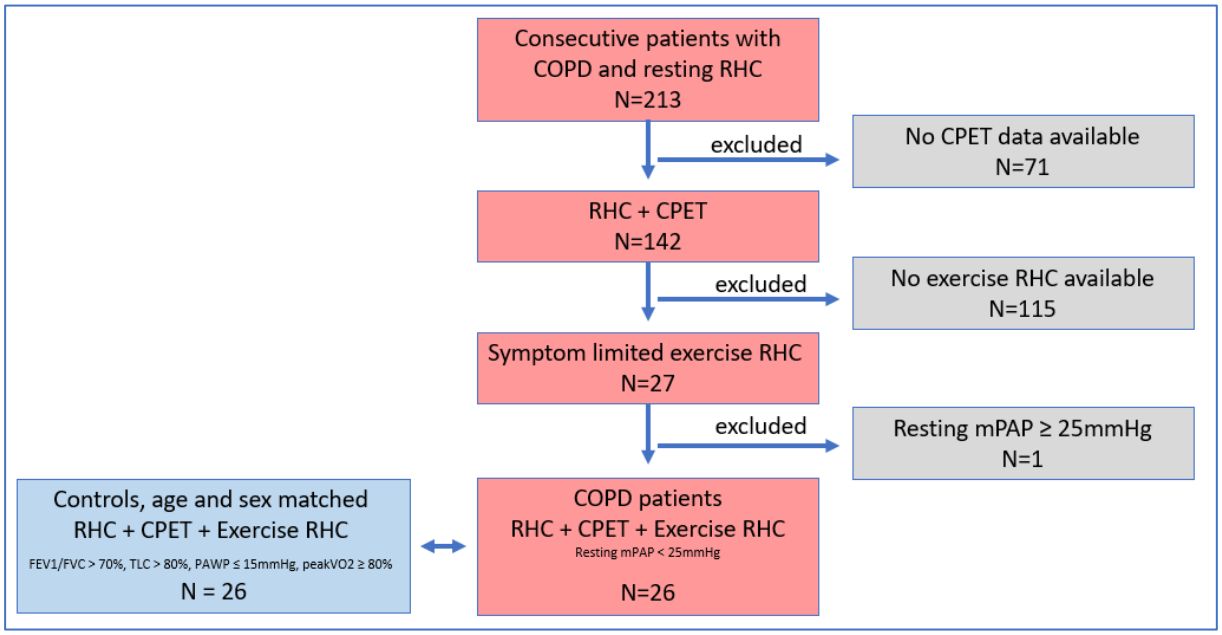


Figure 10 Flow chart of the COPD patients and controls

3.1.1 Baseline characteristics

The mean age was 66 ± 11 years and the majority of the patients and controls was male (62%). There were no significant differences concerning body mass index (BMI), blood pressure, WHO-FC and laboratory data between the two groups (Table 9).

Variable	COPD Patients N=26	Controls N=26	p-value
Age, years	66 ±11	66 ± 10	p=0.990
Sex, (female/male)	16/10 (62%/38%)	16/10 (62%/38%)	p=0.990
BMI, kg/m²	24 ± 5	26 ± 4	p=0.060
Systolic blood pressure, mmHg	126 ± 19	129 ± 18	p=0.458
Diastolic blood pressure, mmHg	66 ± 11	68 ± 12	p=0.469
WHO-FC I/II/III/IV	1/16/7/2 4%/62%/27%/8%	4/16/6/0 15%/62%/23%/0%	p=0.098
Hemoglobin, g/dL	13.6 (12.7-14.9)	14.0 (12.6-14.7)	p=0.880
Creatinine, mg/dL	0.91 (0.70-1.28)	0.97 (0.81-1.07)	p=0.497
GFR, ml/min /1.73 m²	81 (69-95)	85 (46-87)	p=0.211
Uric acid, mg/dL	5.1 (4.8-8.1)	5.6 (5.3-6.9)	
NT-proBNP, pg/mL	263 (101-625)	144 (64 -344)	p=0.109
Bilirubin, mg/dL	0.4 (0.2-0.7)	0.7 (0.5-1.1)	p=0.076
Albumin, g/l	4.2 (3.8-4.3)	4.3 (3.9-4.7)	p=0.714

Table 9 Baseline patient characteristics

3.1.2 Comorbidities

As our patients reflect a real-world cohort, and controls were not healthy per-se, most of the patients suffered from comorbidities (Table 10). All COPD patients (100%) and 18 (69%) controls had at least one comorbidity. Out of the controls, 8 (31%) control patients had no comorbidity, 14 (54 %) had one, three (12 %) had two and one subject (4%) suffered from three comorbidities. Out of the COPD patients 11 (42%) had one, 12 (46%) had two and three (12%) had three or more comorbidities.

Comorbidities		COPD N=26	Controls N=26
Cardiac	Arterial hypertension	10	10
	Atrial fibrillation	5	6
	Coronary artery disease	1	6
	Minor intracardiac shunt	1	1
Pulmonary	Controlled asthma	-	1
	Obstructive sleep apnea	4	1
	Systemic sclerosis with mild pulmonary involvement	2	2
	Chronic thromboembolic disease	0	3
Hepatic	Liver cirrhosis Child A/B/C	1/0/0	0/2/0
Renal	Severe chronic kidney disease (GFR <30 ml/min)	1	2

Table 10 Relevant comorbidities from both groups

In the overall cohort, cardiac comorbidities, and in particular systemic arterial hypertension were the most common, followed by atrial fibrillation and obstructive sleep apnea syndrome. One COPD patient had an atrial septum defect without indication for intervention, and one control patient was status post occlusion of a foramen ovale ten years earlier. The medication of patients and controls are listed in Table 11.

Medication	COPD N=26	Controls N=26
Angiotensin-converting enzyme inhibitors	6 (23%)	5 (19%)
Angiotensin receptor blockers	0 (0%)	3 (12%)
Beta-Blockers	11 (42%)	13 (50%)
Diuretics	10 (38%)	11 (42%)
Digitalis glycosides	1 (4%)	2 (8%)
Levothyroxin	3 (12%)	5 (19%)
Antidepressant drugs	1 (4%)	6 (23%)
Oral anticoagulants	7 (27%)	7 (27%)
Long-term oxygen therapy	5 (19%)	0 (0%)
PAH specific therapy	3 (12%)	0 (0%)
Anti-obstructive therapy	26 (100%)	0 (0%)
Non-invasive Ventilation	1 (4%)	0 (0%)

Table 11 Medical intake of COPD patients and controls

3.1.3 Cardiac function parameters

Echocardiography was performed in 24 subjects, 12 controls and 12 COPD patients. Neither systolic nor diastolic left ventricular function parameters were different between the groups. Interestingly, albeit higher RHC-derived mPAP values at rest in COPD patients, echocardiography-derived TRV and sPAP were not significantly different between the groups. In addition, right ventricular function, estimated by TAPSE was comparable in both COPD patients and controls (Table 13).

Variable	COPD N=12	Controls N=12	p-value
FS (%)	39 (37-47)	32 (30-41)	p=0.18
LVEDD (cm)	44 (38-55)	52 (47-66)	p=0.13
IVSd (mm)	7 (7-10)	9 (7-12)	p=0.786
LVPWd (mm)	10 (9-11)	10 (8-11)	p=0.24
LA (cm²)	35 (29-41)	38 (35-43)	p=0.307
E (cm/s)	0.66 (0.55-0.75)	0.7 (0.66-0.98)	p=0.418
A (cm/s)	0.88 (0.71.-0.95)	0.85 (0.67-0.99)	p=0.426
E/E‘ (mean)	10 (7-11)	12 (8-15)	p=0.242
TRV (m/s)	32 (27-37)	32 (26-45)	p=0.776
RAP (cm)	5 (5-5)	5 (5-9)	p=0.325
SPAP (mmHg)	39 (33-42)	37 (31-50)	p=0.644
TAPSE (cm)	24 (18-27)	25 (21-27)	p=0.419

Table 13 Echocardiographic parameters

3.1.4 Pulmonary related parameters

Within the COPD group, five (19%) patients were in Gold-stage I, 13 (50%) in Gold-stage II, three (12%) in Gold-stage III and five (19%) in Gold-stage IV (Figure 11). Out of these patients, five patients received long-term oxygen therapy.

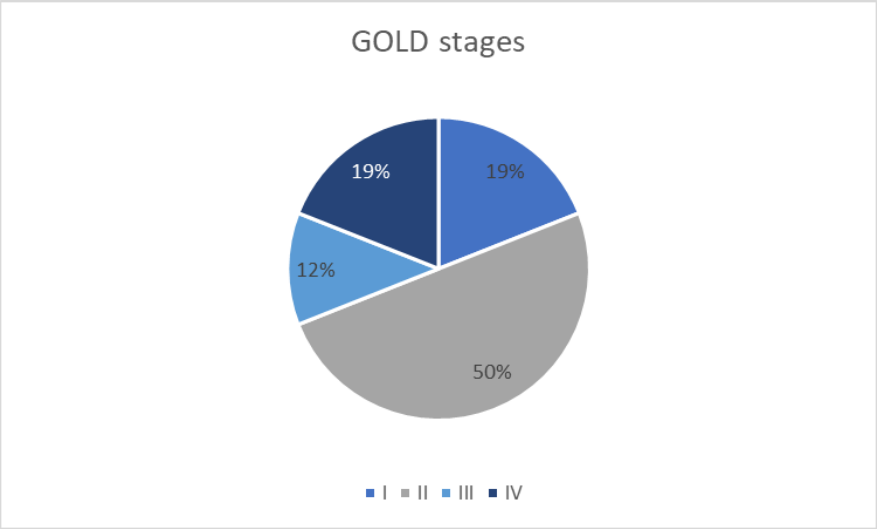


Figure 11 GOLD stages of the COPD group

In terms of smoking activity, there was no significant difference between the groups. Although COPD patients had more packyears (py) than controls, this did not reach statistical significance (25 (11-33) py vs. controls 15 (9-30) py, p=0.323). As expected, COPD patients presented with abnormal lung function parameters compared to the control group. Moreover, both groups revealed similar values of arterialized partial pressure of oxygen (PaO_2), arterialized partial pressures of carbon dioxide ($PaCO_2$), oxygen saturation (SpO_2) and arterio-venous oxygen content differences ($AVDO_2$) (Table 14).

Variable	COPD Patients N=26	Controls N=26	p-value
Smoking status never/quit/active	7/15/4	12/12/2	p=0.314 p=0.323
FVC, % predicted	74 ± 25	101 ± 23	p=0.001
FEV1, % predicted	56 ± 25	96 ± 22	p<0.001
FEV1/FVC	60 (50-66)	78 (73-82)	p<0.001
TLC, % predicted	123 ± 31	104 ± 12	p=0.025
DLCOcSB, % predicted	59 ± 19	83 ± 18	p<0.001
DLCOcVA, % predicted	74 ± 22	89 ± 17	p=0.007
PaO_2, mmHg	68 (59-78)	68 (64-86)	p=0.558
$PaCO_2$, mmHg	39 (36-42)	33 (30-35)	p=0.256
SpO_2, %	95 (93-97)	95 (94-98)	p=0,528
$AaDO_2$, Vol%	3.7 (2.7-5.1)	4.9 (3.5-6.0)	p=0.749

Table 14 Lung function and BGA related parameters

3.2 Exercise capacity

As expected, due to the inclusion criteria of the control group, controls revealed normal peakVO_2 values, while in COPD patients, peakVO_2 was significantly reduced (64 (55-82) % predicted vs. controls 95 (87-102) % predicted) (Figure 12).

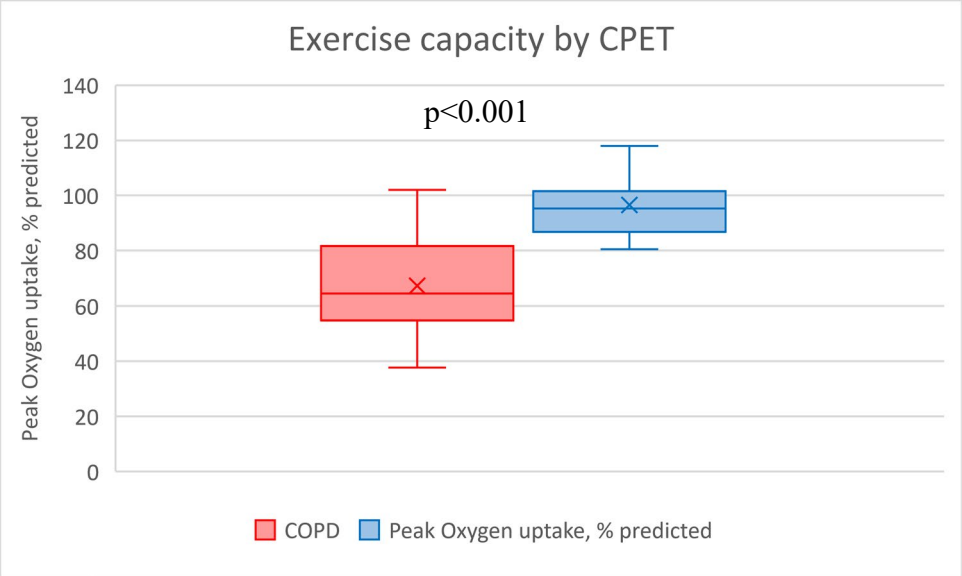


Figure 12 CPET in COPD vs. controls

During exercise, COPD patients reached significantly lower maximal work load levels compared to controls (50 (50-75) watt vs. 100 (75-125) watt, p=0.002). Finally, also the 6MWT reflected a decreased exercise performance of the COPD group vs. the control group (360 (308-434) m vs. 447 (394-493) m, p=0.018) (Figure 13).

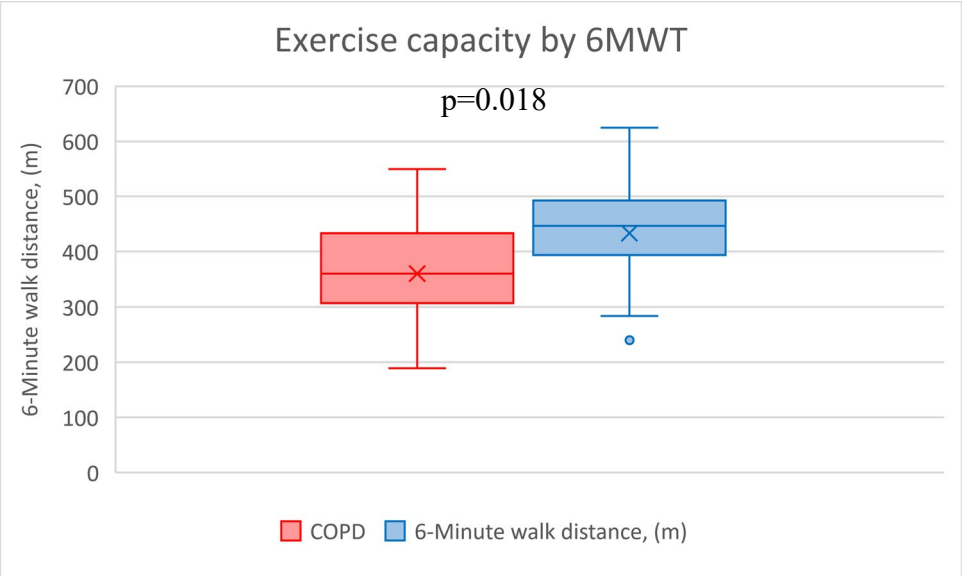


Figure 13 6MWT in COPD patients vs. controls

3.3 Pulmonary hemodynamics at rest

At rest, COPD patients showed slightly elevated mPAP (21 (18-23) mmHg vs. 17 (14-20) mmHg, p=0.022), PVR (2.5 (1.9-3.0) WU vs. 1.9 (1.5-2.4) WU, p=0.035) and TPR (4.3 (3.8-5.7) WU vs. 3.5 (2.7-4.4) WU, p=0.007) as compared to the control group. However, in PAWP, RAP, CO, pulmonary arterial compliance and pulmonary arterial stiffness, there were no significant differences between the groups (Table 14).

Variable	COPD N=26	Controls N=26	p-value
mPAP, mmHg	21 (18-23)	17 (14-20)	p=0.022
PAWP, mmHg	8 (6-10)	8 (6-10)	p=0.789
RAP, mmHg	5 (3-6)	5 (4-6)	p=0.492
PVR, WU	2.5 (1.9-3.0)	1.9 (1.5-2.4)	p=0.020
TPR, WU	4.3 (3.8-5.7)	3.5 (2.7-4.4)	p=0.007
CO, L/min	4.4 (3.8-5.8)	4.5 (4.0-5.3)	p=0.742
CI, L/min/m²	2.6 (2.3-3.1)	2.6 (2.3-2.8)	p=0.782
PVC, mL/mmHg	3.7 (2.7-5.0)	4.0 (3.0-5.1)	p=0.351
PA stiffness index, mmHg/m²/mL	0.50 (0.37-0.62)	0.45 (0.35-0.59)	p=0.023

Table 15 Hemodynamic parameters at rest

3.4 Pulmonary hemodynamics during exercise

During physical activity, compared to controls, COPD patients had impaired peak VO_2 and 6MWD, despite lower maximal exercise levels as compared to controls (Figure 12 and Figure 13). Every subject was able to complete the 25 Watt level. At this submaximal exercise level, COPD patients reached significantly higher mPAP (36 (30-41) mmHg vs. 29 (21-35) mmHg; p=0.025) and TPR (5.2 (4.1-7.3) WU vs. 3.9 (3.1-5.1) WU; p=0.024) values, compared to controls (Table 15).

Variable	COPD N=26	Controls N=26	p-value
mPAP, mmHg	36 (30-41)	29 (21-35)	p=0.025
PAWP, mmHg	13 (11-23)	13 (11-17)	p=0.302
RAP, mmHg	8 (6-13)	7 (4-11)	p=0.271
PVR, WU	3.0 (1.9-4.0)	2.2 (1.2-2.6)	p=0.110
TPR, WU	5.2 (4.1-7.3)	3.9 (3.1-5.1)	p=0.024
CO, L/min	6.6 (5.3-8.5)	7.0 (5.8-8.4)	p=0.323
CI, L/min/m²	3.7 (3.2-4.7)	3.8 (3.4-4.6)	p=0.534
PVC, mL/mmHg	4.3 (2.4-5.5)	3.6 (2.5-6.2)	p=0.607
PA stiffness index, mmHg/m²/mL	0.84 (0.70-1.11)	0.61 (0.42-1.00)	p=0.442

Table 16 Pulmonary hemodynamics at 25 Watt.

A total of 44 subjects, 20 COPD patients and 24 controls completed the 50 Watt level. During 50 Watt, differences between the groups became even more pronounced compared to the resting values with mPAP (46 (39-51) mmHg vs. 31 (24-41) mmHg; p= 0.006), TPR (5.4 (4.2-6.6) WU vs. 3.7 (2.7-4.8) WU; p=0.013) in COPD vs. control patients. While at rest and during 25 Watt of exercise level, neither PVC nor PA stiffness index were differed between the groups, at 50 Watt level however, COPD patients compared to controls revealed significantly lower PVC (2.0 (1,7-2.5) mL/mmHg vs. 3.6 (2.4-4.5) mL/mmHg; p=0.010) and higher PA stiffness index (0.84 (0.72-1.05) mmHg/m²/mL vs. 0.53 (0.41-0.77) mmHg/m²/mL; p=0.023) (Table 16).

Variable	COPD N=26	Controls N=26	p-value
mPAP, mmHg	46 (39-51)	31 (24-41)	p=0.006
PAWP, mmHg	19 (12-26)	16 (12-21)	p=0.203
RAP, mmHg	12 (9-17)	9 (5-13)	p=0.068
PVR, WU	2.8 (1.9-3.5)	1.8 (1.1-2.5)	p=0.053
TPR, WU	5.4 (4.2-6.6)	3.7 (2.7-4.8)	p=0.013
CO, L/min	8.1 (7.1-9.7)	8.6 (7.8-10.0)	p=0.273
CI, L/min/m²	4.6 (4.3-5.5)	4.9 (4.4-5.3)	p=0.396
PVC, mL/mmHg	2.0 (1,7-2.5)	3.6 (2.4-4.5)	p=0.010
PA stiffness index, mmHg/m²/mL	0.84 (0.72-1.05)	0.53 (0.41-0.77)	p=0.023

Table 17 Pulmonary hemodynamics at 50 Watt

At individual peak exercise, however, the differences of pulmonary hemodynamics between COPD patients and controls were most prominent with mPAP (47 (40-52) mmHg vs. 38 (32-44) mmHg; p=.0.015), PVR (3.1 (2.2-3.7)) WU vs. 1.7 (1.1-2.9) WU; p=0.028) and TPR (5.7 (4.5-7-0) WU vs. 3.8 (2.6-5.2) WU; p=0.005), although peak workload was reduced in COPD. During peak exercise, COPD patients reached significantly lower cardiac output (7.8 (7.0-10.9) L/min vs. 10.3 (8.1–13.5) L/min; p= 0.004) and cardiac index (4.7 (4.2-5.7) L/min/m² vs. 6.2 (4.5-7.9); p=0.034) than controls, despite similar resting CO and CI values. RVOR was significantly decreased in COPD patients as compared to controls (0.9 (0.5-1.2) vs. 1.3 (0.7-1.8), p=0.020) (Table 17). Of note, neither at rest nor at any exercise level, there were any group differences between COPD patients and controls concerning PAWP and RAP.

Variable	COPD N=26	Controls N=26	p-value
mPAP, mmHg	47 (40-52)	38 (32-44)	p=0.015
PAWP, mmHg	20 (15-28)	20 (15-25)	p=0.495
RAP, mmHg	14 (8-18)	11 (7-14)	p=0.165
PVR, WU	3.1 (2.2-3.7)	1.7 (1.1-2.9)	p=0.028
TPR, WU	5.7 (4.5-7-0)	3.8 (2.6-5.2)	p=0.005
CO, L/min	7.8 (7.0-10.9)	10.3 (8.1–13.5)	p=0.044
CI, L/min/m²	4.7 (4.2-5.7)	6.2 (4.5-7.9)	p=0.034
PVC, mL/mmHg	1.9 (1.6-2.6)	3.0 (2.0-4.4)	p=0.045
PA stiffness index, mmHg/m²/mL	0.84 (0.70-1.11)	0.61 (0.42-1.00)	p=0.056
RVOR ($CI_{exercise-rest}/CI_{rest}$)	0.9 (0.5-1.2)	1.3 (0.7-1.8)	p=0.020

Table 18 Pulmonary hemodynamics at individual peak exercise

In terms of pressure-cardiac output-slopes, COPD patients, compared to controls, had significantly steeper slopes with mPAP/CO (6.9 (5.0-10.9) mmHg/L/min vs. 3.7 (2.4-7.4) mmHg/L/min, p=0.007), PAWP/CO-slopes (COPD: 2.9 (1.9-6.4) vs. 1.8 (1.3-4.2) mmHg, p=0.051), RAP/CO (2.3 (1.3-4.2) mmHg/L/min vs. 1.2 (0.5-2.1) mmHg/L/min, p=0.025) and TPG/CO (3.5 (1.6-4.5) mmHg/L/min vs. 1.6 (0.9-3.5) mmHg/L/min, p=0.048) (Figure 14 and Table 18).

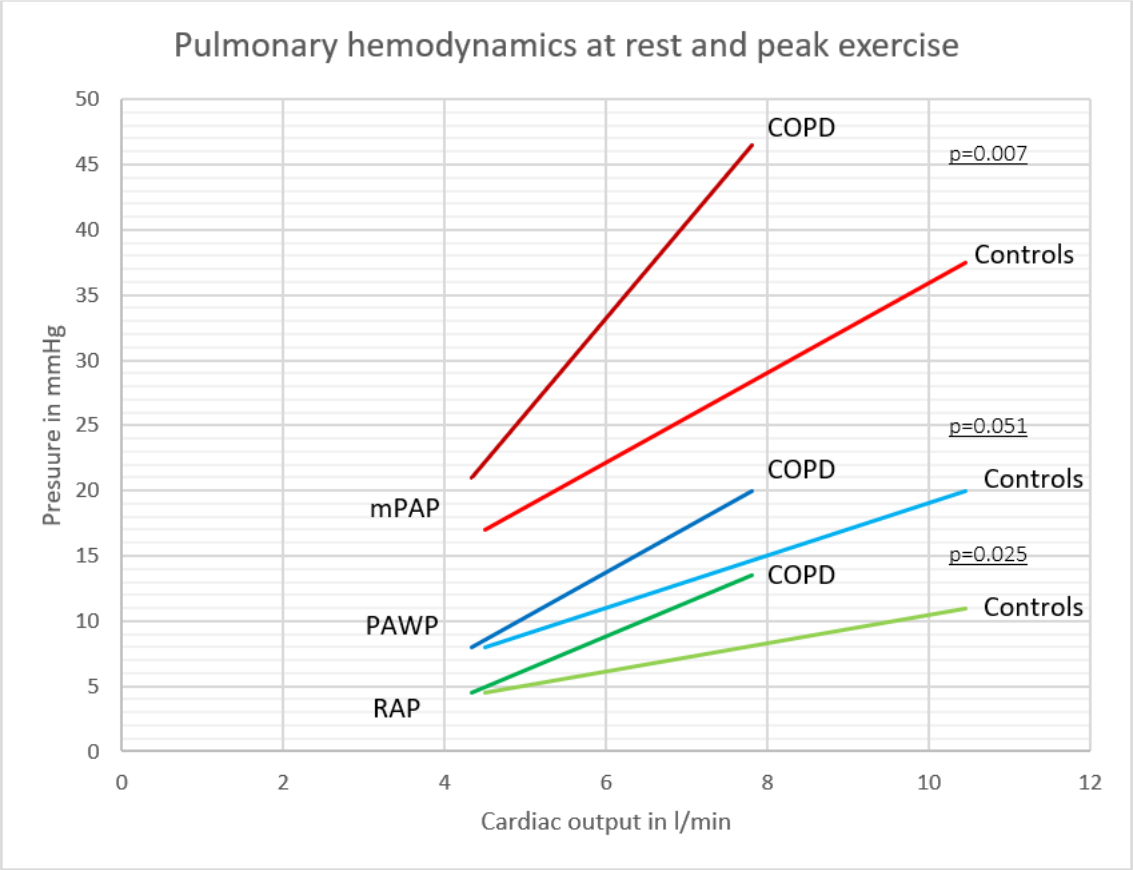


Figure 14 Pressure/cardiac output slopes in COPD vs. controls [1]

According to the 2022 ERS/ESC guidelines for the diagnosis and treatment of PH, 24 (92%) COPD patients and 16 (62%) controls fulfilled the criteria of EPH. Thereof, 18 (75%) COPD patients and 9 (56%) controls, respectively had a PAWP/CO slope >2 WU and therefore a potential precapillary component.

Variable	COPD N=26	Controls N=26	p-value
mPAP/CO slope, mmHg/L/min	6.9 (5.0-10.9)	3.7 (2.4-7.4)	p=0.007
PAWP/CO slope, mmHg/L/min	2.9 (1.9-6.4)	1.8 (1.3-4.2)	p=0.051
RAP/CO slope, mmHg/L/min	2.3 (1.3-4.2)	1.2 (0.5-2.1)	p=0.025
TPG/CO slope, mmHg/L/min	3.5 (1.6 – 4.5)	1.6 (0.9-3.5)	p=0.048

Table 19 Pressure/cardiac output slopes of COPD vs. controls

3.5 Association between exercise capacity and pulmonary hemodynamics

While at rest only mPAP (r_ρ: -0.461; p=0.007) and TPR (r_ρ=-0.389; p=0.025) were correlated to peak VO_2, during exercise mPAP (r_ρ: -0.445; p=0.009), TPR (r_ρ: -0.422; p=0.016) and additionally PVR (r_ρ: -0.517 ; p=0.003), PVC (r_ρ: 0.490 ; p=0.004) and PA stiffness index (r_ρ: -0.562 ; p=0.001) showed a significant association to peak VO_2. None of the resting pulmonary hemodynamic values was correlated to 6MWT, however, at individual peak exercise, 6MWT showed a correlation with CI (r_ρ: 0.542; p<0.001), TPR (r_ρ: -0.432; p=0.003) and PVC (r_ρ: 0.301; p=0.047). RVOR was positively correlated both to peak VO_2 (r_ρ: 0.492; p=0.004) and 6MWT (r_ρ: 0.577; p<0.001). Peak VO_2 was significantly associated with the mPAP/CO slope (r_ρ=-0.459, p=0.007 and the TPG/CO slope (r_ρ=-0.423; p=0.014), while 6MWT was negatively correlated to mPAP/CO slope (r_ρ= -0.464; p=0.001) and PAWP/CO slope (r_ρ=-0.547; p<0.001) (Table 19).

Value	Peak VO_2 (% predicted)		6 minute walk test (m)	
	Spearman correlation	p-value	Spearman correlation	p-value
Resting meanPAP, mmHg	-0.461	p=0.007	-0.145	p=0.338
Resting PAWP, mmHg	-0.126	p=0.485	0.071	p=0.920
Resting RAP, mmHg	0.042	p=0.817	0.015	p=0.487
Resting CI, L/min/m²	-0.222	p=0.241	-0.105	p=0.095
Resting TPR, WU	-0.389	p=0.025	-0.249	p=0.109
Resting PVR, WU	-0.318	p=0.072	-0.239	p=0.639
Peak meanPAP, mmHg	-0.445	p=0.009	-0.019	p=0.901
Peak PAWP, mmHg	0.052	p=0.776	-0.204	p=0.184
Peak RAP, mmHg	-0.264	p=0.138	0.116	p=0.441
Peak CI, L/min/m²	0.337	p=0.055	0.542	p<0.001
Peak TPR, WU	-0.422	p=0.016	-0.432	p=0.003
Peak PVR, WU	-0.517	p=0.003	-0.155	p=0.333
Peak PVC, mL/mmHg	0.490	p=0.004	0.301	p=0.047
Peak PA stiffness index, mmHg/m²/ml	-0.562	p=0.001	-0.260	p=0.089
RVOR, L/min/m²	0.492	p=0.004	0.577	p<0.001
mPAP/CO slope, mmHg/L/min	-0.459	p=0.007	-0.464	p=0.001
PAWP/CO slope, mmHg/L/min	-0.189	p=0.293	-0.547	p<0.001
RAP/CO slope, mmHg/L/min	-0.331	p=0.064	-0.215	p=0.155
TPG/CO slope, mmHg/L/min	-0.423	p=0.014	-0.173	p=0.250

Table 20 Correlations of exercise capacity with pulmonary hemodynamics [1]

In Figure 15, the most relevant correlations between CPET derived peak VO_2 and 6MWT with mPAP/CO slope (panel A/B), pulmonary vascular compliance (PVC) (panel C/D) and right ventricular output reserve (RVOR) (panel E/F) are shown. COPD patients are represented with red dots and control subjects with green dots.

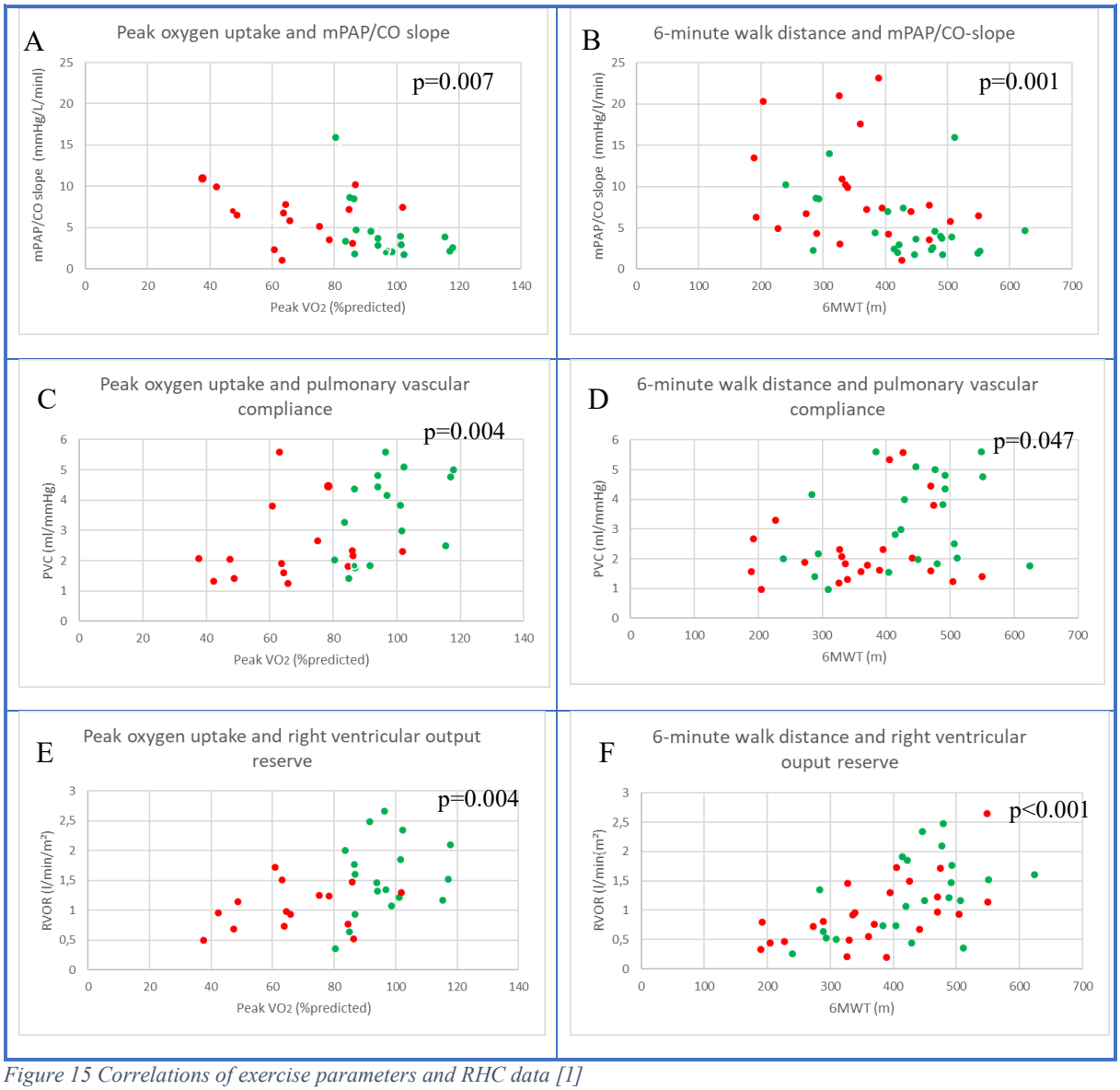


Figure 15 Correlations of exercise parameters and RHC data [1]

3.6 Outcome related Data

The median follow-up time was 89 (43-125) months. During the observation period 17 (65 %) of the COPD patients and 9 (35%) of the controls died (Figure 16).

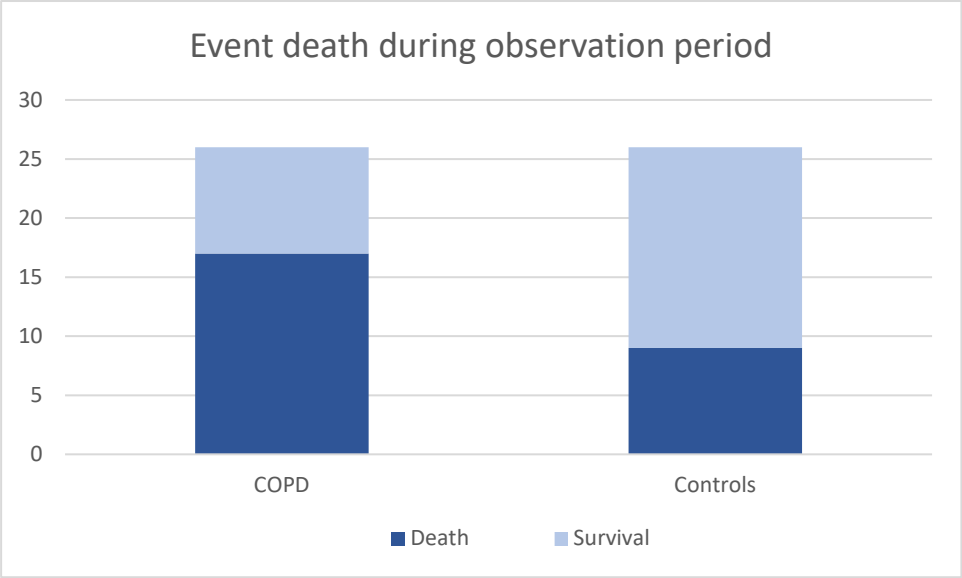


Figure 16 Bar graph of survived and died subjects

Additionally, the median observation time of 10 years of the two groups is shown by Kaplan Maier curves in Figure 17. Although, a separation of the two graphs after 8 years can be observed visually, due to limited power, few events and inclusion critera, we abstained from performing univariate and multivariate Cox regression models and further survival analysis.

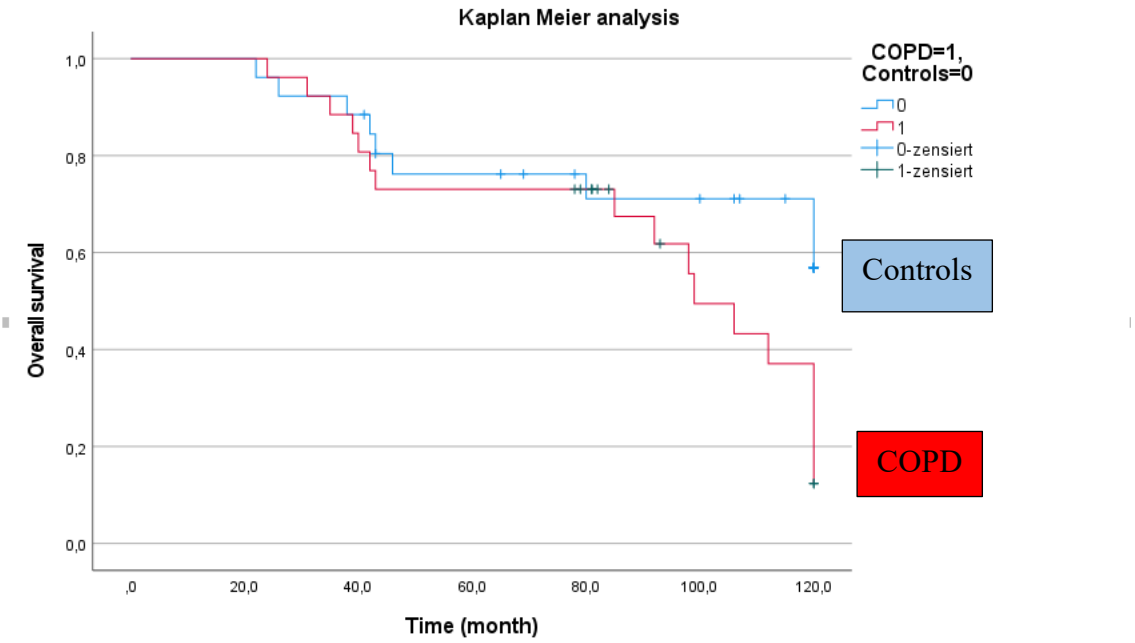


Figure 17 Kaplan Meier curves for overall 10-years survival.

Furthermore, a cumulative endpoint of disease-related hospitalization and all-cause-mortality was analyzed. A total of 18 (69%) COPD patients and 7 (27%) controls had a disease related hospitalization (Figure 18).

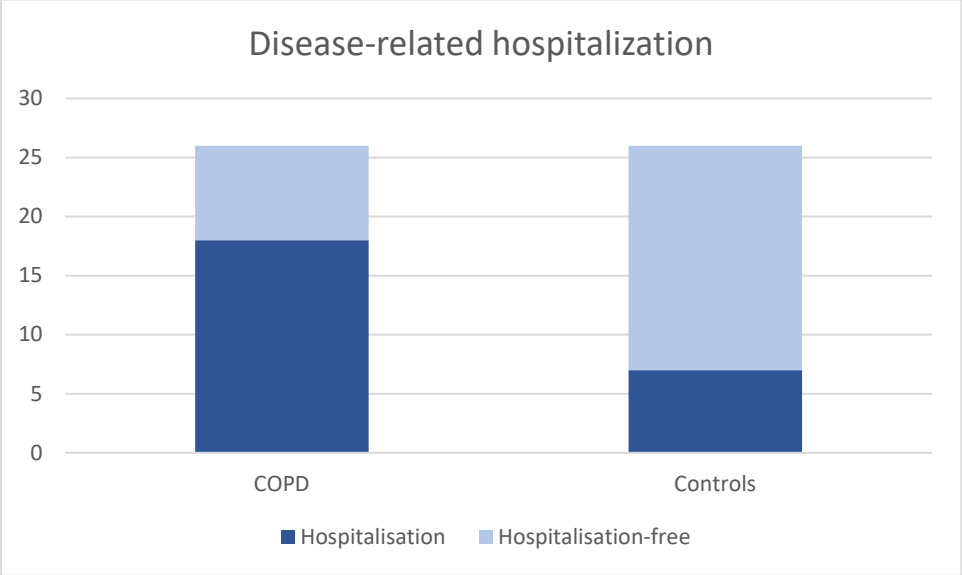


Figure 18 Bar graph of subjects with and without hospitalization

Kaplan Maier curves show 10-years cumulative endpoint, hospitalization or death, of the two groups. As above mentioned, we abstained from performing univariate and multivariate Cox regression models and further survival analysis for reason of limited power, few events and inclusion criteria (Figure 19).

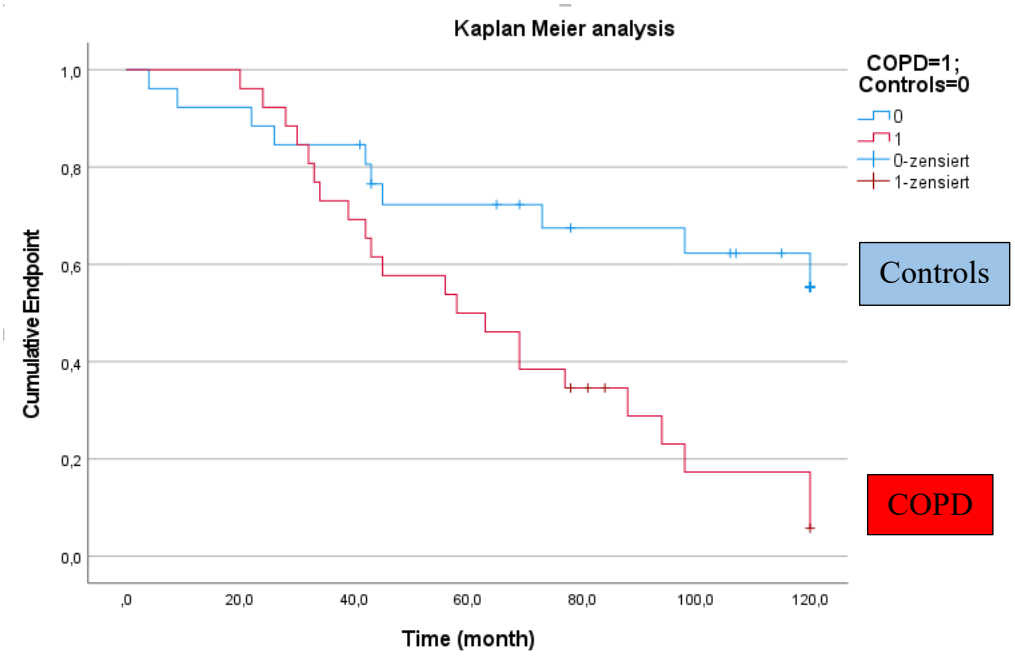


Figure 19 Kaplan Meier curves for cumulative endpoint of disease-related hospitalization or death after 10 years

Out of the cases of death, most COPD patients (N=7; 41%) died due to the underlying pulmonary disease, five (29%) due to cardiovascular events and one (6%) subject had a fatal gastrointestinal bleeding event. The remaining four (24%) patients died for reasons, that were not identifiable. Controls died due gastrointestinal bleeding (N=2; 22%), septic shock (N=1; 11%), pulmonary embolism (N=1; 11%), aortic valve stenosis (N=1; 11%), liver disease (N=1; 11%), myelodysplastic syndrome (N=1; 11%) and others (N=2; 22%).

For disease-related hospitalization, we included acute infections, exacerbation of COPD with or without pneumonia, progressive dyspnea, and relevant pulmonary or cardiac disease.

4 Discussion

In this study, we retrospectively analyzed a collective of COPD patients at risk for PH with unexplained dyspnea, despite optimized anti-obstructive therapy and compared them to age and sex matched controls without significant pulmonary diseases. In particular, we focused on invasive exercise hemodynamics and exercise testing to better characterize this subgroup of patients. Therefore, patients underwent 6MWT, CPET and RHC at rest and during exercise besides basic clinical investigation.

Mainly we found that COPD patients, even without relevant pulmonary hypertension at rest, show characteristic abnormalities in pulmonary hemodynamics during exercise, compared to age- and sex-matched controls without chronic lung disease. In addition, the prevalence of exercise pulmonary hypertension in this COPD collective was very high. COPD patients were markedly limited in their exercise performance, that was associated with invasive exercise hemodynamics. Albeit normal right heart function at rest, COPD patients revealed significantly lower right ventricular output reserve at exercise compared to controls. Based on these and previous findings, we consider the responses to physical exercise in COPD patients with no or very mild PH as characteristically abnormal.

4.1 Definition and prevalence of exercise pulmonary hypertension in COPD

The relevance of exercise hemodynamics in order to describe pulmonary circulatory disorders is discussed since 1960 [14]. However, it took one decade until Hatano et al. stated in 1973 that during exercise, the mPAP does normally not exceed 30 mmHg [5]. From then, three more decades passed by, until in 2004, exercise PH (EPH) was defined as exercise mPAP >30 mmHg in guidelines of the European Society of Cardiology [15].

Later, it was highlighted in a systematic review with approximately 1200 subjects, that mPAP alone is not appropriate to describe EPH as the impact of age on exercise hemodynamics and normal changes in CO is not addressed adequately [7]. Therefore, a sufficient discrimination between physiological and pathological hemodynamic pattern during effort was not possible and the definition of EPH was henceforward removed from the guidelines [6,16].

In the following years, several attempts have been made to reintroduce EPH in order to find early stages of PVD, which are potentially better treatable. However, this time authors focused on other hemodynamic patterns. Based on the knowledge that mPAP increases with increasing blood flow, studies were performed, including the pressure/CO-slopes [5,107]. By using pressure/CO-slopes, authors were able to show the prognostic impact of EPH of mPAP/CO-slope which led to the reintroduction of EPH of mPAP/CO slope > 3 mmHg/L/min in the recent guidelines [87,90,108]. In addition, its prognostic value was shown to be independent from pulmonary hemodynamics at rest [89].

Only few data exist about the prevalence of EPH in COPD patients. On the one hand this is due to the different definition of EPH in the last decades. On the other hand, the interest of investigating pulmonary hemodynamics at exercise in COPD patients grew in the last years, as suspicion of a pulmonary vascular phenotype was risen and pathological exercise hemodynamics were supposed to be a potential precursor of COPD-PH [68]. In a study by Portillo et al. in 2015, the prevalence of EPH, based on this threshold, was 71% (60/85) [88]. In 2018, Skjørten et al. found in their COPD collective of 93 stable outclinic patients an EPH prevalence of 45%.

In comparison to these data, the prevalence of EPH in our COPD cohort was very high (92%). This might be due to the limited number of investigated subjects and/or due to the fact, that for ethical reasons, indication for invasive RHC is very strict at our study place as patients have to have suspicion for PH. In consideration of the high frequency of COPD and the prognostic relevance of EPH, the impact of EPH on the underlying disease should not be neglected and further studies are necessary to determine the prevalence of EPH in COPD.

4.2 Response to exercise in COPD patients

Due to ethical reasons, hemodynamic data of healthy subjects are limited, however, a few studies provided data of normal response to exercise. Already in 1964, Granath et al. stated a mPAP/CO-slope of 2.8 mmHg/L/min to be normal in their cohort of "healthy old man" (age 71 ± 6 years). A few years later, in 1971, Degré et al. reported a mPAP/CO slope of 1.5 mmHg/L/min in healthy persons, however, these participants were much younger (age 41 ± 4.8 years) [109]. In a study by Lewis et al. in 2011, a healthy cohort (age 60 ± 12 years) showed a mPAP/CO slope of 1.4 mmHg/L/min during exercise to be normal [110]. Kovacs et al. reported in a systematic review in 2011 of 1.187 healthy subjects from 47 studies that mPAP alone is not sufficient to define abnormal responses to exercise due to a strong age-dependency on PAP and a strong impact of CO [7]. In a recent systematic review, in 2022, Zeder et al. confirmed that the mPAP/CO-slope is strongly dependent on age and its upper limit of normal ranges from 1.6–3.3 mmHg/L/min [91].

In comparison to these studies on healthy subjects, our data indicate an obvious pathological response to exercise (mPAP/CO-slope 6.9 (5.0-10.9) mmHg/L/min) in COPD patients without or only mild PH which was significantly higher compared to our age-and sex- matched controls. Of note, also our control group exceeded the upper limit of normal (mPAP/CO slope 3.7 (2.4-7.4) mmHg/L/min) as they were not healthy individuals. The huge difference of mPAP/CO-slope between both groups, however, characterizes the abnormal response to exercise in COPD patients.

Until now, there are only few studies investigating the pulmonary hemodynamic response to cardiopulmonary exercise in patients with COPD, though this knowledge of hemodynamic response to stress might help to reveal the pathophysiology of exertional dyspnea during physical activity, despite optimally treated airway obstruction.

In a first study conducted by Burrows et al. in 1972, in 50 COPD patients an abnormal steep elevation of mPAP in relation to CO during invasive exercise RHC was found [81]. The authors concluded, that COPD patients with relatively mild obstruction and without relevant hypoxemia but dyspnea during physical activity preserve at rest their mPAP and CO, however, at exercise the abnormalities of the pulmonary vascular bed become more obvious. They randomly

included all COPD patients who agreed to undergo RHC due to scientific reasons and who had no congestive heart failure or an acute exacerbation. Further comorbidities were not named or investigated.

In another study by Portillo et al. in 2015, exercise hemodynamics in 85 COPD patients were retrospectively investigated. The authors found abnormal vascular responses to exercise (defined by mPAP: <50 years: >30 mmHg; ≥50 years: >46 mmHg and mPAP/CO slope > 3 mmHg/L/min, respectively) in the majority of patients, even in those with mild airflow obstruction, and concluded that pulmonary vascular destruction is an early event in the natural history of COPD [88].

Hilde et al. described a strong increase in mPAP/CO slope on effort in 98 COPD patients without PH (4.55 ± 3.33 mmHg/L/min) and with PH (7.17 ± 4.88 mmHg/L/min), $p<0.05$. TPG/CO slope significantly increased in non-PH vs. PH (2.57 ± 2.43 mmHg/L/min vs. 4.71 ± 3.83 mmHg/L/min, $p<0.05$), while PVR only showed a significant elevation in the COPD-PH group [89]. They concluded that the response to exercise in non-PH as well as PH-COPD patients is abnormal. The collective was free of relevant cardiac comorbidities but of note, all patients except of three had emphysema. Despite these differences in patient selection, our results confirm the previous findings.

Compared to the COPD patients of Hilde et al., our COPD cohort revealed a pathologically high mPAP/CO slope with values, that were closer to the COPD-PH than the non-PH group in terms of mPAP/CO slope (mPAP/CO slope 6.9 (5.0-10.9) mmHg/L/min and TPG/CO slope 3.5 (1.6 – 4.5) mmHg/L/min respectively). This is probably due to the fact that their non-PH group showed lower resting mPAP (18 ± 3 mmHg) and their PH-group had higher mPAP (29 ± 4 mmHg) than our COPD cohort (mPAP: 21 (18-23) mmHg).

This leads to the conclusion that there is a continuum of worsening pulmonary exercise hemodynamics with increasing resting mPAP and progression of these abnormalities may lead to the development of PH and explain severe dyspnea at low exercise levels [87].

4.3 Phenotypes of exercise pulmonary hypertension

A steep increase in mPAP/CO slope can be caused by many reasons. EPH represents the hemodynamic appearance of early pulmonary vascular disease, left heart disease, pulmonary disease or a combination of these conditions [92]. Therefore, the discrimination between pre- and postcapillary component still remains challenging. For patients with chronic left heart disease due to heart failure with or without preserved ejection fraction or singular left ventricular diastolic dysfunction mPAP/CO slope is usually driven by an abnormal increase in PAWP. Reeves et al. demonstrated in healthy subjects a two-fold greater contribution of PAWP than TPG to abnormal mPAP rise at exercise [107]. Kovacs et al. reported, that both PVR and TPR are usually slightly reduced during exercise for reasons of passive recruitment and vasodilatation of the pulmonary vascular circulation [13]. In contrast, patients with a precapillary component might reveal an increase in TPG, TPR and/or PVR [68].

In a study conducted by Maor et al. in 2015, increased exercise PAWP was associated with left ventricular and left atrial sizes in patients with exertional dyspnea, preserved left ventricular ejection fraction and suspected PH, highlighting the impact of exercise hemodynamics in unmasking left ventricular diastolic dysfunction [111]. A peak exercise PAWP $\geq$ 25 mmHg is associated with heart failure with preserved ejection fraction in subjects with exertional dyspnea and normal resting PAWP and was therefore included in the current recommendation to diagnose heart failure with preserved ejection fraction of the European Society of Cardiology [112,113]. However, PAWP/CO slope was independently associated with prognosis in a study conducted by Ho et al. in 2020 [87]. In the same year, Bentley et al. analyzed 85 patients with dyspnea and/or suspected PH and compared them to 36 healthy controls. They demonstrated that abnormal pulmonary arterial pressure responses in EPH patients are not driven by left heart filling abnormalities if PAWP/CO slope was $\leq$2 mmHg/L/min [114]. Eisman et al performed a study with 110 patients with exercise induced dyspnea and normal PAWP at rest and found a PAWP/CO slope >2 WU with a prevalence of 40%. In addition, this threshold was associated with adverse clinical outcomes, in particular cardiovascular death, hospitalization due to left heart failure or elevated resting PAWP in a following RHC [115].

As a consequence of these results, a PAWP/CO slope >2 WU was considered to be prognostically relevant in patients with heart failure with preserved ejection fraction despite

normal resting PAWP and better describes hemodynamic processes during exercise than PAWP alone. Most recently, it was shown that pulmonary exercise hemodynamics including mPAP/CO slope, PAWP/CO slope and TPG/CO slope predict all-cause mortality independently from pulmonary exercise hemodynamics in a general patient collective at risk for PVD [90]. This underlines the additive value of pulmonary exercise hemodynamics.

Otherwise, an increase in PAWP can also occur in COPD patients due to other mechanisms than left heart disease. In 1998 Butlers et al. investigated exercise pulmonary hemodynamics in 39 COPD patients with moderate to severe airflow limitation (FEV1 39 ± 16%) and compared them to controls without obstruction but with similar mildly elevated mPAP values at rest [116]. The authors found a major increase in PAWP in COPD patients during physical activity. They explained this finding on the one hand due to hyperinflation causing rise in intrathoracic pressures and underlined this suspicion with spirometry and chest-ray data during physical activity. On the other hand, they assumed PAWP increase at exercise to occur due to normal elevation in end-diastolic left ventricular transmural pressure according to the Frank Starling mechanism that is expected with increasing CO. In 2001 Chabot et al. reported high PAWP during exercise in COPD subjects and explained this by the intrathoracic pressure rise due to lower lobe air trapping in those COPD patients with the most severe airflow limitation [117]. Finally also respiratory variability can cause increase in PAWP due to huge thoracic excursions during hyperventilation in relation to stable zero reverence level [116]. In 2014, Kovacs et al. summarized, that positive expiratory intrathoracic pressure in COPD may be explained by active expiratory muscle contraction and dynamic hyperinflation that further increases functional residual capacity resulting in a decreased venous return, which might affect PAP. During exercise, this phenomenon is even pronounced, because exhalation may not be completed when the next breath starts. This might lead to increasing amounts of trapped air at end-exhalation. They concluded, that also the measurement results in an overestimation of pulmonary vascular pressures in case of end-expiratory measurements due to pulmonary pressures hyperventilation and airway obstruction which might explain the elevated PAWP in patients with severe emphysema [104].

Finally, not only PAWP but also RAP is affected by air trapping during exercise and consequently increasing intrathoracic pressures in COPD patients. Therefore, in these patients

RAP increase is an indicator of intrathoracic pressure and can further contribute to steep mPAP/CO slope, although exact numbers are lacking [68,118].

Mechanisms of EPH in COPD patients have only been rarely investigated and are not fully understood. Herve et al. showed in their study 2015 that a total pulmonary resistance (TPR) >3 WU is able to distinguish between diseased and control patients, but failed to discriminate between left heart disease and PVD. In addition this group found, that adding TPR to mPAP at peak exercise improves sensitivity from 0.98 to 0.93 and specificity from 0.77 to 1.0. [119]. Burrows et al reported in 50 COPD patients an abnormally steep increase of PVR during invasive exercise RHC, that was associated with survival in these patients. They concluded, that exercise unmasks the abnormalities of the pulmonary vascular bed of those COPD patients with only mild airway obstruction but severe dyspnea during exercise. In a study by Hilde et al. on 98 COPD patients, TPG/CO slope significantly increased in non-PH vs. PH (2.57 ± 2.43 mmHg/L/min vs. 4.71 ± 3.83 mmHg/L/min, $p<0.05$), while PVR only showed a significant elevation in the COPD-PH group [89]. Kubo et al. reported a strong correlation between pulmonary arterial wall thickening and invasive peak exercise mPAP of COPD patients undergoing lung volume reduction surgery [120]. These results suppose also abnormalities in pulmonary vascular in COPD patients and therefore support the hypothesis of a pulmonary vascular phenotype. However, until now and based on all these studies the threshold of PAWP/CO slope of 2 WU was the best parameter to distinguish between pre-and postcapillary PH and was hence included in the current guidelines [2,114,115].

In this study, we assessed the changes in PAWP, TPG and RAP during exercise to further investigate the underlying reason of increase in mPAP/CO slope in this COPD cohort. Compared to controls, we found that all pressure/CO slopes (PAWP/CO slope, RAP/CO slope and TPG/CO slope) were steeper in COPD patients. This leads to the assumption that precapillary as well as postcapillary factors and an additionally elevated intrathoracic pressure contribute to abnormal pulmonary exercise hemodynamics in COPD.
According to the recent definitions, 69% of our COPD patients and 35% of the controls, respectively had a PAWP/CO slope >2 WU and therefore a potential postcapillary component. In elderly patients, an increased PAWP/CO slope might indicate the existence of left ventricular diastolic dysfunction as part of a physiological aging process [121]. As our cohort was 66 ± 11

years old, this is a potential reason of abnormal increase in mPAP/CO slope at exercise. In addition, as mentioned before, a steep PAWP/CO slope and RAP/CO slope may also be driven by hyperdynamic inflation during exercise in these patients. Finally, due to our strict zero-reference level protocol, we pay a lot of attention to the wright position and average pulmonary pressures over a minimum of at least three respiratory cycles. Therefore, errors in measurements can never be completely avoided, but reduced to a minimum. Taking this into account, we assume that false high or low PAWP and RAP values in this study were unlikely.

Besides PAWP- and RAP slopes, in our cohort TPG/CO slope contributed most prominently to the mPAP/CO slope in COPD patients. This inverse relation of contribution of more TPG/CO slope than PAWP/CO slope to the mPAP/CO slope, suggests a precapillary component as leading cause for an abnormal hemodynamic response to exercise in COPD patients with very mild PAP elevation. The TPG/CO slope is supposed to be age independent and considered to be normal below approximately ≤ 1.2 WU, a value that our COPD cohort exceeded by far [91]. The results support the assumption of early pulmonary vascular involvement in COPD which is unmasked by physical training. In a study by Hilde et al. TPG rather than PAWP increases contributed to pressure slope increases in COPD-PH as well as COPD-non-PH subjects, however, RAP was not investigated [89]. Furthermore, a markedly drop in pulmonary vascular compliance relative to the change in PVR during exercise was found. Finally, Saouti et al. proposed that a small increase in PVR at exercise accompanied by a huge drop in pulmonary arterial compliance might be a hallmark of early changes in the pulmonary vascular system [122]. In the current study we also made similar observations. While at rest, there was no significant difference between COPD and controls, at peak exercise there was a significant drop of PVC in the COPD group, while controls almost maintained their PVC. Therefore, with our data we could not only confirm observations of Hilde and Saouti et al., but also, provide a complete characterization of pulmonary hemodynamics compromising a decline of PVC linked with abnormal pressure increase in relation to CO, driven by potentially three components of precapillary, postcapillary and intrathoracic pressure abnormalities PVC during exercise in COPD.

4.4 Clinical relevance of abnormal pulmonary exercise hemodynamics

The clinical relevance of exercise hemodynamics has only rarely been investigated in patients with COPD, although it may give information about the pathophysiology of exercise dyspnea, and provides additional information beyond resting pulmonary hemodynamics in several clinical situations.

Firstly, COPD patients of the current study were markedly limited in their exercise capacity by means of 6MWT and CPET-derived peak VO_2 and maximal workload. That COPD patients with PH are limited in their exercise capacity has been known for many years [123,124]. However, the pathophysiology of exercise limitation of non-PH COPD patients might exceed ventilatory limitation, especially in patients under optimal anti-obstructive treatment, who suffer from disproportional dyspnea at physical activity. Indeed, we found that peak VO_2 was not only significantly correlated to the resting mPAP and TPR, but also to peak mPAP, PVR, TPR, PAC and mPAP/CO slope during exercise, indicating that pathological exercise hemodynamics may significantly contribute to exercise limitation in these patients and might explain dyspnea despite optimized bronchodilative therapy. With that, we were able to confirm data of previous studies. Skjørten et al. reported high frequency of exercise limitation in COPD patients and abnormal pulmonary exercise hemodynamics with an disproportionate increase of mPAP/CO slope exceeding 3 mmHg/L/min at physical activity [125]. In another study by Hilde et al. that investigated COPD subjects 6MWD was negatively associated with resting mPAP (r= -0.55; p,0.01) and PVR (r= -0.6; p,0.01), even after adjustment for age, gender, height, weight, FEV1 and PAWP. During exercise, an approximately 10 m decrease for every mmHg elevation of mPAP and a 30 m decrease for every WU elevation of PVR was observed (95% CI: -14.3– -4.5 m; p,0.01 and 95% CI: -48.9– -10.1 m; p,0.01 respectively) [89]. Additionally, maximum workload was strongly associated with both PVR and PAC at peak workload (r= -0.7; p= 0.01 and r= 0.5, respectively; p,0.01). Furthermore, the wall thickness of pulmonary vessels in COPD patients who were screened to undergo lung volume reduction surgery was strongly associated with mPAP during exercise (r=0.721, p=0.02) and delta $mPAP_{exercise-rest}$ (r=0.899, p=0.0004) [120]. These results clearly indicate early pulmonary vascular involvement in COPD patients additionally contributing to exercise limitation in these patients.

According to recent data, healthy subjects usually reveal mPAP/CO slopes of 1.6-3.3 mmHg/L/min, while mPAP/CO slope exceeds 3 mmHg/L/min in patients with early PVD [87,91]. A mPAP/CO slope >3 mmHg/L/min was independently correlated to survival in patients with preserved ejection fraction but chronic dyspnea during daily activity [87]. In patients with scleroderma a mPAP/CO slope of ≥ 2.9 mmHg/L/min was associated with age-adjusted mortality and a mPAP/CO slope >3 mmHg/L/min a predictor of transplant-free survival [108,126]. With a mPAP/CO slope of 6.9 mmHg/L/min the COPD patients exceeded the prognostic relevant cut-off of 3 WU by far, suggesting a markedly abnormal pulmonary hemodynamic response to exercise.

Whether an elevated mPAP/CO slope affects mortality in COPD patients, has not been investigated so far, although it has been assumed. Finlay et al showed in 1983 in 74 COPD patients with cor pulmonale that increase of mPAP and PVR at exercise are predictors of clinical deterioration [127]. Olsen et al. reported a significantly increased risk of postoperative mortality within 60 days or prolonged ventilation for more than 30 days in patients with COPD undergoing lung resection due to airflow obstruction in case of low peak CO at exercise [128]. Both our controls and COPD subjects were sex matched, at the same age, revealed comparable comorbidities and had suspicion for PH due to exercise dyspnea. Nevertheless, 10-years survival rates were apparently lower in the COPD group than in the controls. However, due to limited power, few events and inclusion criteria, we abstained from performing univariate and multivariate Cox regression models and further survival analysis. Therefore, it remains unclear whether resting-, exercise hemodynamics and/or ventilatory limitation affected outcome of this COPD cohort. Further studies with more power are required to provide answers to this research question.

Patients with EPH are of increased risk to develop PH in the long run, as exercise mPAP above 30 mmHg is a marker of disease progression [122]. In terms of hospitalization, a mPAP/CO slope >3 mmHg/L/min was independently associated with hospitalization in chronic exertional dyspnea patients with preserved ejection fraction [87]. Moreover, in a study by Wells et al. dilatated pulmonary arteries by computed tomography, were shown to be better predictors of exacerbations in COPD patients than any other lung function parameter [26]. When showing 10-years cumulative endpoint of the groups with Kaplan Meier curves, our COPD patients had

seemingly worse disease-related hospitalization rate or death compared to controls. Again, we did not perform univariate and multivariate analysis to correct for pulmonary function parameters because of too poor power. However, in consideration of the results of this study and the former studies, abnormal pulmonary hemodynamics may be indicative for clinical events in COPD.

Not only mPAP/CO slope but also an increased TPG/CO slope > 1.2 WU was associated with impaired survival and increased risk of cardiovascular events [87,91,108]. An abnormally high TPG/CO slope may be additionally suggestive of PVD [129–131]. With 3.5 (1.6 – 4.5) mmHg/L/min the TPG/CO slope of our COPD cohort was almost 3-fold higher than the supposed upper limited of normal, indicating an early pulmonary vascular involvement in our COPD cohort.

An increased PAWP/CO >2 WU is considered to be abnormal and was shown to be associated with increased mortality and cardiovascular events [87,115]. It may further advocate the existence of a post-capillary cause of abnormal increase of pulmonary pressures during exercise [115]. In the current study, PAWP/CO slope was 2.9 (1.9-6.4) mmHg/L/min in the COPD subjects, therefore exceeding the threshold. That COPD patients are at increased risk of cardiovascular events, especially of acute myocardial infarction, has been reported, however, it remains unclear whether PAWP/CO slope is a predictor of cardiovascular events in COPD, too [132].

4.5 Right heart function in COPD

Apart from the involvement of pulmonary vessels, right ventricular function is of clinical relevance in COPD. In 1963 an expert committee of the World Health Organization defined, "cor pulmonale" as right ventricular hypertrophy due to diseases affecting the pulmonary function and/or pulmonary structure [14]. Nevertheless, COPD is by far the leading cause of cor pulmonale. The assessment of both prevalence and mortality related to cor pulmonale is challenging, as there might be a huge estimated number of unreported cases and whether ventilatory or cardiac issues are the leading reason of death is usually difficult to discriminate [133]. In COPD, chronic alveolar hypoxia, marked morphological lung parenchyma changes, loss of pulmonary capillaries and pulmonary vascular remodeling are the major cause of elevated PVR and pulmonary pressures. Cor pulmonale is therefore a consequence of pulmonary functional and structural changes, causing elevation of pulmonary pressures and resistances leading to chronic right heart stress, causing initially hypertrophy, in later stages dilation and right heart failure. The progression from PH to manifest right heart failure is slow in COPD with a stable mPAP value for three up to twelve years [134,135]. In a study by Weitzenblum et al. 93 COPD patients without and with PH (PAP > 20 mmHg) were followed up during approximately 8 years. Within the observation period, mPAP changed only +0.5 mmHg/year in both COPD patients with and without initial PH [136]. Nevertheless, patients with severe COPD can exhibit a rapid worsening of PH, which is associated with poor prognosis. Despite normal resting values, during severe exacerbations, right ventricular contractility can be markedly decreased in COPD causing severe dyspnea and peripheral edema in these patients affecting clinical outcome [137]. Today, the term cor pulmonale has more historical meaning as the term was more or less replaced by the term pulmonary hypertension associated with lung disease [2].

Changes in right heart function and its adaptation to increased afterload are supposed to be of prognostic importance in COPD patients. In a study conducted by Grünig et al. in 2013 authors showed that COPD patients with better right ventricular contractile reserve, assessed by stress echocardiographic derived change of sPAP from baseline to peak exercise, revealed significantly better exercise capacity by means of 6MGT and peak oxygen uptake via CPET as well as superior survival [138]. Ghio et al. reported in 2010 that echocardiographic assessed right heart function was associated with mortality in patients with idiopathic PAH [139].

Five years later, similar observations were made by Spruijt et al. who showed that manifest PH patients are unable to increase their contractile reserve during exercise, defined by response in end-systolic elastance (ΔEes) from rest to exercise and the effects of exercise on the matching of Ees to right ventricular afterload (Ea). Although this was a study with only few investigated patients, complex invasive using single-beat pressure-volume loops were conducted and therefore contributed to a high quality of this study. Even early signs of RV failure may be associated with poor outcome [138–142].

RVOR reflects the adaptation capability of the right ventricle in order to increase CO during exercise. In our COPD patients, RVOR was significantly reduced as compared to controls (0.9 L/min/m² compared to 1.3 L/min/m², p=0.02). Therefore, we assume a limited right ventricular reserve during exercise in these patients. Moreover, RVOR was strongly associated with both peak VO_2 and 6MWD. Therefore, our results were at least comparable to those of Grünig et al. who showed a reduced exercise tolerance in COPD patients when right ventricular contractile reserve was reduced. However, in their study, echocardiographic values were used as measure of RV contractility. In a study by Nagel et al. reduced PAC during physical activity and reduced right ventricular output reserve accounted for impaired 6-minute walking distance in patients with systemic scleroderma and only mildly elevated mPAP [129]. In a recently conducted study by Xanthouli et al. of 280 patients with systemic scleroderma at risk for PH RVOR during exercise < 2 l/min was a predictor of survival ($p<0.0001$) [143]. With 0.9 (0.5-1.2) l/min, our COPD cohort went clearly below that limit. In summary together with former studies, the results suggest an important impact of RVOR to exercise limitation and survival in COPD. Larger prospective studies are required to provide more reliable answers to this topic.

4.6 Limitations

The relatively low number of analyzed subjects and the retrospective nature are obvious limitations of our study. This limitation may partly be compensated by the invasive hemodynamic characterization by experienced investigators that was performed in every single patient.

For reasons of visualization, we showed Kaplan Meier curves of 10-years survival and cumulative endpoint of either all-cause mortality or hospitalization. As before mentioned, we abstained from performing univariate and multivariate survival and multiple-endpoint analysis, because of limited power, few events and for reasons of the inclusion criteria of the control group. Nevertheless, the obvious associations of pulmonary exercise hemodynamics with exercise capacity highlight the clinical relevance of pulmonary hemodynamics during exercise in patients with COPD with no or only mild PH. As our patients represent a real-world cohort, they were not free of comorbidities. However, COPD patients with severe and potentially exercise limiting comorbidities were not included into this study. Systolic and diastolic blood pressure was normal in both groups and there was no significant difference in systolic and diastolic blood pressure between the groups. All subjects with atrial fibrillation had normal resting heart rate.

Finally, a further limitation is the absence of a ”true” healthy control group. Therefore, EPH in our controls was still quite frequent (62%). Furthermore, this was a selected collective, as all subjects underwent invasive exercise RHC due to suspicion of PH and disproportional dyspnea, as invasive RHC cannot be performed in healthy people due to ethical reasons.

5 Conclusions

This study aimed to gain further information of the mechanisms of exercise limitation and hemodynamic response to physical stress in COPD patients in the absence of marked PH but with severe exertional dyspnea despite optimal anti-obstructive therapy. We aimed to contribute to a better understanding of the pathophysiological mechanisms of early pulmonary vascular involvement in COPD patients. Therefore, we retrospectively analyzed COPD patients without PH or with only mildly elevated resting pulmonary arterial pressure who underwent invasive exercise RHC and compared them to age-and sex- matched controls. We found that even in the absence of relevant pulmonary hypertension, COPD patients reveal characteristic abnormalities in pulmonary hemodynamics, reduced pulmonary vascular compliance and impaired right ventricular function during exercise. These exercise parameters, in contrast to most resting values, were all associated with exercise limitation, highlighting a significantly contribution to their exercise limitation and providing a potential reason for the disproportional dyspnea on exertion of these patients. Larger prospective studies are warranted to validate these findings.

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