

Dissertation

Clinical relevance of mildly elevated pulmonary arterial pressure

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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”.

Philipp Douschan

Graz, November 2019

Disclosures

Parts of the results of this thesis were published as full paper in January 2018 in the American Journal of Respiratory and Critical Care Medicine (1). Data, tables and figures from this publication used within the thesis were reprinted with permission of the American Thoracic Society (Copyright © 2019 American Thoracic Society).

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All co-authors declare that they have no conflicts of interest with the content of this thesis and have explicitly agreed to use their data in the thesis. Doctoral candidate Philipp Douschan was trained within the frame of the Doctoral School of Molecular Medicine and Inflammation of the Medical University of Graz.

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Abbreviations and Definitions

6MWD	six-minute walking distance
6MWT	six-minute walking test
APAH	associated PAH
AT	anaerobic threshold
BPD	bronchopulmonary dysplasia
CCB	calcium channel blocker
CF	cystic fibrosis
cGMP	cyclic guanosine monophosphate
CI	cardiac index
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CpcPH	combined pre- and postcapillary PH
CPET	cardiopulmonary exercise testing
CPFE	combined pulmonary fibrosis and emphysema
CTED	chronic thromboembolic pulmonary disease
CTEPH	chronic thromboembolic pulmonary hypertension
CW- doppler	continuous wave doppler
DLCOc SB	single breath diffusion capacity of CO adjusted for hemoglobin
DLCOc	diffusion capacity for CO adjusted for hemoglobin and

VA	alveolar volume
dPAP	diastolic pulmonary arterial pressure
EPH	exercise PH
FEV1	forced expiratory volume at 1 second
FVC	forced expiratory vital capacity
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HIV	human immunodeficiency virus
HP	hypersensitivity pneumonitis
HPAH	hereditary PAH
HR	heart rate
IPAH	idiopathic PAH
IpcPH	isolated post capillary PH
IPF	idiopathic pulmonary fibrosis
LAM	lymphangiomyomatosis
LCH	Langerhans cell histiocytosis
LPS	lipopolysaccharide
LVEDP	left ventricular end-diastolic pressure
LVEF	left ventricular ejection fraction
MET	metabolic equivalent
mPAP	mean pulmonary arterial pressure

PAH	pulmonary arterial hypertension
PAWP	pulmonary arterial wedge pressure
PBA	pulmonary balloon angioplasty
PDE5	phosphodiesterase 5
PEA	pulmonary endarterectomy
peakVO ₂	oxygen uptake at maximum work load
PETCO ₂	end-tidal PCO ₂
PETO ₂	end-tidal PO ₂
PGI ₂	prostaglandin I ₂
PH	pulmonary hypertension
PKG	proteinkinase G
POPH	portopulmonary hypertension
PVD	pulmonary vascular disease
PVOD	pulmonary veno-occlusive disease
PVR	pulmonary vascular resistance
PVRI	pulmonary vascular resistance index
RAP	right atrial pressure
RER	respiratory exchange ratio
RHC	right heart catheterization
RR	respiratory rate
RV	residual volume

SD	standard deviation
sGC	soluble guanylate cyclase
SMC	smooth muscle cells
sPAP	systolic pulmonary arterial pressure
SVR	systemic vascular resistance
SVRI	systemic vascular resistance index
TKI	tyrosine kinase inhibitor
TLC	total lung capacity
TPR	total pulmonary resistance
TRV	tricuspid regurgitation velocity
VC	vital capacity
VCO ₂	carbon dioxide output
VD	Deadspace
VE	minute ventilation
VE/VCO ₂	respiratory equivalent CO ₂
VE/VO ₂	respiratory equivalent for O ₂
VO ₂	oxygen uptake
VO ₂ /HR	oxygen pulse
VT	tidal volume
WHO	World Health Organization
WU	wood units

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Abstract

Background and aims: Mean pulmonary arterial pressure (mPAP) is 14.0 ± 3.3 mmHg (mean \pm SD) under physiological conditions. As we initiated our study, the definition of pulmonary hypertension (PH) was an elevation of mPAP ≥ 25 mmHg. The clinical relevance of mildly elevated mPAP above 20 mmHg but below 25 mmHg was unclear. Accordingly, we aimed to assess the association of resting mPAP with all-cause mortality in a retrospective and a prospective cohort of patients with unexplained dyspnea and/or at risk of PH with special focus on patients not fulfilling the former hemodynamic criteria of PH.

Methods: Prognostic cut-offs specific for our collective were first calculated by using regression tree (CART) analysis. In a second step mPAP cut-offs from the literature were used: lower-normal mPAP (\leq mean + 1st SD), upper-normal mPAP (between mean + 1st SD and mean + 2nd SD), borderline (between mean + 2nd SD and 25 mmHg), and manifest PH (≥ 25 mmHg). We performed univariate and multivariate survival analysis adjusted for age and comorbidities.

Results: Overall 547 patients were enrolled with 153 patients (26%) prospectively recruited. All patients underwent invasive assessment of pulmonary hemodynamics by means of right heart catheterization (RHC). N = 137, 56, 64 and 290 presented with lower-normal, upper-normal, borderline mPAP and manifest PH, respectively. The CART analysis on mPAP revealed three prognostic groups, mPAP < 17 mmHg, 17 - 26 mmHg, and > 26 mmHg, with significantly decreasing survival. The univariate analysis based on thresholds from the literature showed that upper-normal, borderline mPAP and manifest PH were significantly associated with poor survival, compared to lower-normal mPAP. However, patients with mildly elevated pulmonary pressure were significantly older and had more cardiopulmonary comorbidities. In addition, they presented with lower exercise capacity and higher frequencies of exercise PH. In the multivariate model, corrected for age and comorbidities, only borderline mPAP [HR: 2.37, 95% CI: 1.14 - 4.97 ($p = 0.022$)] and manifest PH [HR: 5.05, 95% CI: 2.79 - 9.12 ($p < 0.001$)] were significantly associated with poor survival.

Conclusion: In a combined retro- and prospective cohort at risk for PH and/or with unexplained dyspnea, unbiased CART analysis revealed prognostic cut-offs at a resting mPAP of 17 mmHg and 26mmHg. A mPAP between 20 mmHg and 25 mmHg represents an independent predictor of poor survival. Based on our results together with findings from other studies the definition for pulmonary hypertension was changed to mPAP > 20 mmHg at the 6th World Symposium on Pulmonary Hypertension in Nice, 2018.

Kurzfassung

Hintergrund und Ziele: Unter physiologischen Bedingungen beträgt der mittlere pulmonalarterielle Druck (mPAP) 14 ± 3 mmHg. Vor Durchführung dieser Studie war Lungenhochdruck durch einen mPAP ≥ 25 mmHg definiert. Inwiefern leichtgradig erhöhte pulmonale Drücke, welche noch nicht die hämodynamischen Kriterien für eine pulmonale Hypertonie (PH) erfüllen, von klinischer Relevanz sind, war bis dahin nicht vollständig geklärt. Ziel dieser Studie war es daher zu prüfen, ob ein Zusammenhang zwischen dem mPAP und der Gesamtmortalität in einem Kollektiv aus retrospektiven- sowie prospektiv rekrutierten Patienten besteht. Ein besonderer Schwerpunkt lag auf dem möglichen Einfluss von leichtgradig erhöhten pulmonalen Drücken.

Methoden: Prognostische mPAP Grenzwerte wurden zum einen mittels Regressions-Baum-Analyse (CART) ohne zuvor gewählte Cut-offs berechnet, zum anderen erfolgten Analysen basierend auf bereits bekannten mPAP Grenzwerten aus der Literatur: niedrig-normaler mPAP (\leq Mittelwert [MW] + 1. Standardabweichung [SA]), hoch-normaler mPAP (zwischen MW + 1. SA und MW + 2. SA), borderline mPAP (zwischen MW + 2 SA und 25 mmHg), manifeste PH (≥ 25 mmHg). Es erfolgten univariate sowie multivariate Überlebensanalysen, welche auf das Alter und das Vorhandensein von kardiopulmonalen Komorbiditäten korrigiert wurden.

Ergebnisse: Insgesamt wurden 547 PatientInnen eingeschlossen von welchen 153 PatientInnen (26%) prospektiv rekrutiert wurden. Anhand des mittels Rechtsherzkatheter ermittelten mPAP ergab sich folgende Verteilung im untersuchten Kollektiv: niedrig-normaler mPAP (N = 137), hoch-normaler mPAP (N = 56), borderline mPAP (N = 64) und manifeste PH (N = 290). Die CART Analyse ergab drei prognostisch unterschiedliche Gruppen: mPAP < 17 mmHg, $17 - 26$ mmHg und > 26 mmHg. Die univariate Überlebensanalyse basierend auf den aus der Literatur bekannten mPAP Grenzwerten zeigte, dass die hoch-normale- und borderline mPAP Gruppen im Vergleich mit PatientInnen mit einem niedrig-normalen mPAP ein signifikant schlechteres Überleben hatten. Allerdings waren PatientInnen mit hoch-normalem- und borderline mPAP signifikant älter, litten an mehr kardiopulmonalen Komorbiditäten. Zudem waren diese Patienten weniger belastbar

und wiesen häufiger einen Lungenhochdruck unter Belastung auf. Die multivariate Überlebensanalyse, korrigiert auf das Alter und die Komorbiditäten, ergab, dass erst ein borderline mPAP [HR: 2.37, 95% CI: 1.14 - 4.97 ($p = 0.022$)] und eine manifeste PH [HR: 5.05, 95% CI: 2.79 - 9.12 ($p < 0.001$)] mit einer signifikant schlechteren Prognose assoziiert sind.

Schlussfolgerung: In einem Patientenkollektiv mit Risiko für die Entwicklung einer PH und/oder unklarer Dyspnoe ergab eine CART Analyse prognostische Grenzwerte bei einem mPAP von 17 mmHg und 26 mmHg. Borderline mPAP stellte sich als unabhängiger Prädiktor für eine schlechte Prognose heraus. Folglich wurde auf der 6. Weltkonferenz für PH in Nizza, 2018, die hämodynamische Definition der PH auf einen mPAP > 20 mmHg geändert.

Introduction

The pulmonary circuit is hemodynamically characterized by high flow and low resistance. Accordingly, significantly lower pressures are present in the right ventricle and the pulmonary circulation as compared to the left ventricle and the systemic circulation. Therefore, an acute or chronic increase of afterload may lead to right heart failure. Pulmonary hypertension (PH) is a condition defined by elevated pulmonary arterial pressure causing right heart strain. Although the classification of PH underwent several changes within the last years, its hemodynamic definition remained more or less the same over the past decades. Until the 6th World Symposium on PH in 2018 and prior to the publication of this study, PH was defined by an elevation of mean pulmonary pressure (mPAP) ≥ 25 mmHg (2). A broad range of different conditions and diseases either directly affecting the pulmonary vascular system or causing PH by pulmonary venous congestion or structural changes in pulmonary architecture have been described.

Definition of pulmonary hypertension at rest

Pulmonary hypertension was always defined by an elevation of mean pulmonary arterial pressure (mPAP). At the first WHO conference for PH held in 1973 in Geneva, an expert consensus defined PH as a mPAP > 25 mmHg. The reason why the 25 mmHg cut-off value was chosen is not reported. In the first WHO report published by Hatano et al. it was stated that under physiological conditions the mPAP normally does not exceed 15 mmHg and almost never exceeds 20 mmHg. Accordingly, PH may be definitely present in patients with a mPAP > 25 mmHg (3). Later on, this cut off was slightly changed and according to the current guidelines PH has been defined by a mPAP ≥ 25 mmHg. Whether or not a mPAP between 20 mmHg and 25 mmHg should be considered pathological remained unclear. The term “borderline mPAP” was used by some groups for the mPAP interval between 21 mmHg and 25 mmHg but was never introduced in the official definitions. Consequently, all following studies focusing on epidemiology and treatment of PH and PAH were based on the 25 mmHg cut-off. Registries dealing with pulmonary vascular disease and their prognostic relevance were therefore limited by preselection of patients with most advanced pulmonary vascular disease (4–7).

Based on data from these preselected patient cohorts right ventricular function rather than mPAP was identified as predictor of mortality.

In 2009, a new attempt was made trying to define what should be considered a normal mPAP. In a study conducted by Kovacs et al., patients with invasive hemodynamic data from 31 studies were analyzed retrospectively. This large meta-analysis revealed that in healthy controls the physiological mPAP is 14.0 ± 3.3 mmHg (mean \pm SD). The physiological mPAP found was very close to the previously reported mPAP of 15 mmHg considered physiological in the initial statement at the first WHO conference for PH. Accordingly, the upper limit of normal could be found at 20.6 mmHg (mean + 2nd SD). No significant differences dependent on sex or geographic origins were found.

Furthermore, there is growing evidence that a mild elevation of mPAP below the 25 mmHg cut-off is of clinical relevance in a wide spectrum of disease. In a small collective of 64 COPD patients, Kessler et al. found a mPAP > 18 mmHg as predictor for acute COPD exacerbation and hospitalization (8). Moreover, in another retrospective study focusing on COPD, a mPAP of 20 mmHg discriminated between different prognostic groups with significant worse 5- and 7-years survival rates of patients with a mPAP > 20 mmHg (9). A similar pattern was found in a prospective study of 61 consecutive IPF patients. IPF patients with a slightly elevated mPAP ≥ 17 mmHg had a 5-year survival rate of 16.7% vs. 62.2% of patients with a mPAP < 17 mmHg (10). Shortly thereafter, studies also evaluating the relevance of mildly elevated mPAP in patients with PAH and APAH followed. Scleroderma patients within the borderline mPAP seem to be at increased risk to progress towards severe PAH with mPAP ≥ 25 mmHg (11). In addition, mildly elevated mPAP is associated with worse exercise tolerance in patients with systemic sclerosis (12). Most recently an analysis of a large collective of the US Veteran Affairs Health Care System revealed that a mPAP between 19 mmHg to 24 mmHg is associated with significant increase in mortality again challenging the historical definition of PH (13).

However, so far no prospective study has been performed assessing the clinical relevance of mild mPAP elevation below the currently used cut off for the definition of

PH. Moreover, there are no data available from a heterogeneous collective of patients at risk for PH as it is seen in a PH clinic.

Pulmonary hemodynamics during exercise

In 1973, at the WHO meeting on pulmonary hypertension, it was first stated that an increase of mPAP > 30 mmHg during exercise in the absence of elevated mPAP at rest may represent a pathological condition (3). Accordingly, a mPAP > 30 mmHg was considered as exercise-induced pulmonary hypertension. However, within the following decades it was realized that mPAP alone insufficiently defines pathological hemodynamics during exercise due to its dependency on the individual exercise level and age (14). Consequently, the term exercise-induced PH was abandoned at the 4th World Conference in Dana Point (15). Thereafter, new approaches also implementing cardiac output for defining pathological pulmonary hemodynamics during exercise for different diseases were discussed (16–19). In a retrospective analysis including historical healthy controls it was found that a mPAP > 30 mmHg together with a total pulmonary resistance (TPR) > 3 WU may be best in discriminating between healthy subjects and subjects with cardiac or pulmonary vascular disease (20). Alternatively, a mPAP/CO-slope > 3 WU has been proposed (19). Based on these observations the term exercise PH (EPH) was defined by expert consensus as mPAP > 30 mmHg and TPR > 3 WU during exercise (21). Multiple conditions, including left heart disease, chronic obstructive pulmonary disease and early pulmonary vascular disease may cause EPH. Differentiating between these subtypes is challenging as adequate measurement of PAWP and intrathoracic pressures are needed and are often technically demanding.

Classification and Phenotypes of Pulmonary Hypertension

Over the last decades the classification system of pulmonary hypertension and its underlying conditions has been changed several times and refined. At first a classification was used separating pulmonary hypertension into primary and secondary PH. Primary pulmonary hypertension was considered to be a condition primarily affecting pulmonary arteries and leading to an increase of pulmonary resistance. On the contrary, secondary pulmonary hypertension was used as general term for all other conditions that may cause an elevation of pulmonary pressure such

as left heart disease or pulmonary disease. Beginning with the second world conference on pulmonary hypertension in Evian in 1998, a new classification system was established also implementing underlying mechanisms causing an elevation of pulmonary pressure, clinical features and therapeutic options. The Evian classification system was used in the years thereafter and slightly adapted every five years at following PH world conferences. In the most recent classification system, established at the world conference in Nice, 2018, five major groups of PH including several subgroups were defined: 1. pulmonary arterial hypertension (PAH), 2. pulmonary hypertension due to left heart disease, 3. pulmonary hypertension due to lung disease or hypoxic conditions, 4. pulmonary hypertension due to artery obstructions and 5. pulmonary hypertension with multifactorial and/or unclear mechanisms (Table 1) .

1 PAH
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH
1.4 PAH 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 long-term responders to calcium channel blockers
1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
1.7 Persistent PH of the newborn syndrome
2 PH due to left heart disease
2.1 PH due to heart failure with preserved LVEF
2.2 PH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH
3 PH due to lung diseases and/or hypoxia
3.1 Obstructive lung disease

3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders
4 PH due to pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
5 PH with unclear and/or multifactorial mechanisms
5.1 Haematological disorders
5.2 Systemic and metabolic disorders
5.3 Others
5.4 Complex congenital heart disease

Table 1: Nice Classification for PH 2018; PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomas; LVEF: left ventricular ejection fraction;

1. Pulmonary arterial hypertension:

In 1865 a case report was published in one of the most recognised medical journals of that time the “Wochenblatt, Zeitschrift der k.k. Gesellschaft der Ärzte in Wien” entitled “endarteritis pulmonalis deformans” (22). In this report, Dr. Julius Klob first described a condition which became later known as idiopathic pulmonary arterial hypertension (PAH). As shown in Table 1, PAH is currently divided into many different subtypes. All of them share the feature of vasoconstriction and remodelling of pulmonary arteries. In some cases, in situ thrombosis of small pulmonary arteries was described. All these findings are finally causing an elevation in pulmonary arterial resistance causing an increase of pulmonary arterial pressure. Vasoconstriction seems to be mediated by an increased activity of vasoconstrictive mediators (e.g. endothelin 1 via endothelin A receptors, Thromboxan A₂) as well as a decreased production of vasodilative mediators such as prostacyclin. Remodelling is primarily localized in small distal pulmonary arteries with an average diameter < 0.5 mm. The remodelling includes medial hypertrophy due to proliferation of smooth muscle cells (SMC). Besides, perivascular lymphatic infiltrates and adventitial fibrosis may be

seen. Fibroblast- and myofibroblast-proliferation causing intimal fibrosis with collagen deposition lead to occlusion of the vascular lumen (Figure 1 B). Moreover, in some types of PAH including IPAH and portopulmonary hypertension (POPH), so-called plexiform lesions are frequently observed. This histological feature is characterized by small channels within the walls of small pulmonary arteries perhaps reflecting neovascularization of the vessel wall.

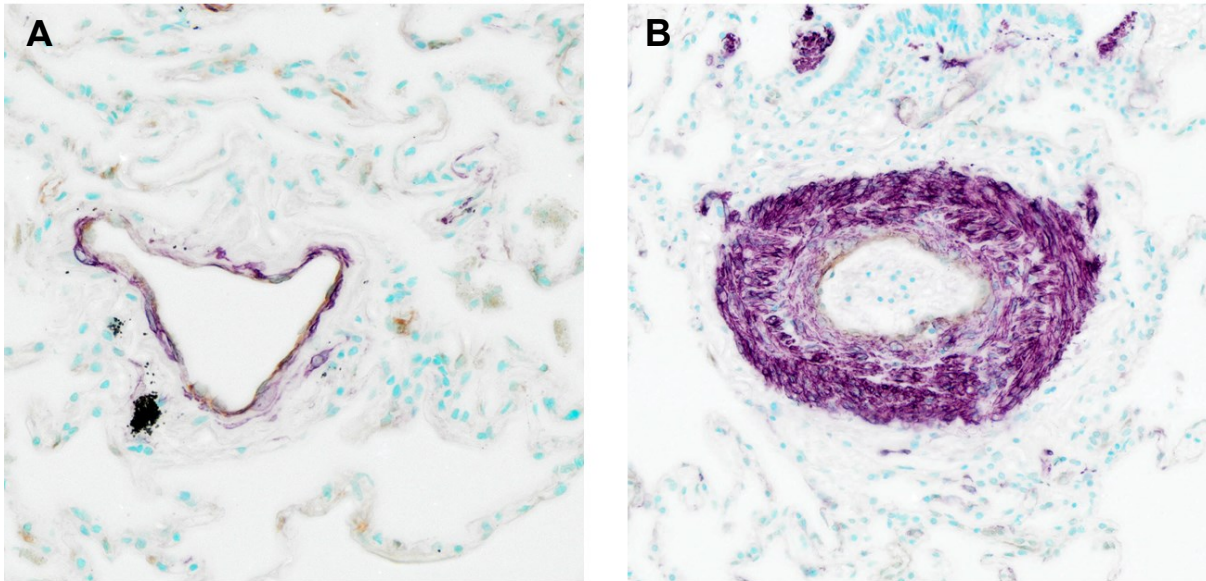


Figure 1: Histological samples of pulmonary arteries; A: normal pulmonary artery, B: pulmonary artery in PAH; HE staining;

The prime example for PAH is idiopathic PAH (IPAH), which is defined as precapillary pulmonary hypertension with no known underlying mechanism or condition. It is a rare (prevalence 5 to 25 cases per million) but severe condition with significant impact on survival (6). It has female predominance. From a clinical point of view it is very difficult to differentiate IPAH from hereditary forms of PAH (HPAH). According to the NIH registry, HPAH accounts for 3% to 6% of all patients diagnosed with PAH (23,24). Genes identified in the context of HPAH are *BMPR2* (25), a member of the $TGF\beta$ family, responsible for tissue growth and inflammatory response, *KCNK3* (26), a potassium channel which may be of importance for pulmonary vasodilation and *CAV1*, a molecule involved in cellular signalling and membrane trafficking (27) and many other gene mutations that are very rare. Besides idiopathic and hereditary forms of PAH, drug-induced types of PAH are known as

well as a large number of other conditions associated with PAH (APAH). In the late nineteen sixties a dramatic increase of newly diagnosed PAH was observed in Austria, Germany and Switzerland. Later on, an association between the onset of this PAH epidemic and the market launch of aminorex fumarate, an appetite suppressant, was found. Clinically and hemodynamically this type of PAH could not be differentiated from IPAH but a clear temporal association with the intake of aminorex was observed (28). Within the last years, several other drugs increasing the risk for PAH were identified including amphetamines (29), selective serotonin reuptake inhibitors (fenfluramine derivatives) (30), specific tyrosine reuptake inhibitors (dasatinib) (31) and specific interferons (32).

Associated pulmonary arterial hypertension (APAH)

Conditions associated with the development of PAH include connective tissue disease, HIV, congenital heart disease, chronic liver disease with portal hypertension and schistosomiasis (33).

PAH in collagen vascular disease

PAH is a frequent finding in collagen vascular disease with highest frequencies reported in scleroderma patients (prevalence of 8% to 12%) (23,34). However, in end stage disease PAH may even affect up to 50% of patients with scleroderma (35). Similar to IPAH, obliteration of pulmonary vessels are key features of PAH in systemic sclerosis. Besides intima proliferation and adventitial fibrosis, endothelial damage or dysfunction seems to play a central role in the pathogenesis of scleroderma-induced PAH as reflected by an elevation of circulating von-Willibrand-factor and circulating vascular cell adhesion molecules (36,37). Moreover, several autoantibodies targeting endothelial cells, fibroblasts, endothelin receptors and angiotensin receptors were detected suggesting autoimmune processes being involved in the pathogenesis of pulmonary vasculopathy (38–40). Although patients with systemic sclerosis show similar or even better pulmonary hemodynamics at the time of diagnosis, their prognosis is significantly worse compared to IPAH patients. 3-year survival rates of less than 60% were reported (33,41). Concomitant interstitial lung disease, pulmonary veno-occlusive disease and cardiac involvement may be additional reasons for poor prognosis (42–44). Other connective tissue diseases

described in the setting of PAH are systemic lupus erythematosus, primary Sjögren syndrome, mixed connective tissue disease and rheumatoid arthritis (33,45–47).

HIV PAH

In the setting of HIV, several abnormal cardiovascular conditions were described including cardiomyopathy and endocarditis. Based on initial case series an association of HIV with PAH was reported (48). Large case control studies and registry data suggested a 1-year-incidence of 0.1% and a prevalence of 0.5% (49,50). Interestingly, the incidence of HIV-PAH dropped within the last decade, perhaps due to an increase in the amount of available combination therapies for HIV. Mechanisms made responsible for the development of HIV PAH are mainly indirect. HIV associated proteins including TAT, Nef and GP120 cause endothelial apoptosis, vascular proliferation and vasoconstriction (51–54). Moreover, dysregulation of intestinal CD4 cells may induce an increased translocation of intestinal lipopolysaccharide (LPS) into the systemic circulation primarily affecting the pulmonary circulation by activation of pulmonary monocytes, macrophages and endothelial cells (55).

PAH in chronic liver disease with portal hypertension

Portal hypertension per se is known to be associated with a wide spectrum of systemic as well as pulmonary hemodynamic abnormalities. In the 19th century, hepatopulmonary syndrome, a condition leading to pulmonary ventilation/perfusion mismatch and hypoxemia was described (56). Besides, PAH may be found in the setting of chronic liver disease with portal hypertension (portopulmonary hypertension [POPH]). First described in a case series in 1951 as extreme endothelial proliferation of pulmonary arteries with embolization, POPH is nowadays reported in 2% to 8% of patients evaluated for liver transplantation. Possible disease mechanisms described in POPH are increased shear stress due to a hyperdynamic circulatory state, an imbalance of vasoconstrictive (ET-1) and vasodilative (prostacyclines, nitric oxide) mediators in the pulmonary circulation and changes in the oestrogen metabolism (57–60). Moreover, a recent study suggested that chronic infection with the hepatitis C virus may induce pulmonary vascular disease and elevation of pulmonary arterial pressure and resistance (61). Again there seems to be a female predominance in

POPH (62–64). Its diagnosis is challenging as other conditions such as hyperdynamic pulmonary circulatory state and left heart disease may also be present in patients with significant portal hypertension (65). Patients diagnosed with POPH seem to have poorer outcome compared to IPAH patients (66,67). Once severe POPH develops, it is considered to be a contraindication for liver transplantation due to the high risk of acute right heart failure after reperfusion of the liver graft (68).

PAH and congenital systemic-to-pulmonary shunts

Congenital left to right shunt is another known risk factor for the development of PAH (69). Chronic exposure to high flow and pressure leads to significant histopathological changes in the pulmonary vasculature including medial hypertrophy, intima- and adventitia thickening. These changes seem to progress until they reach an irreversible state.

PAH and schistosomiasis

Worldwide up to 200 million people are affected by schistosomiasis. Prospective screening studies revealed a prevalence of PAH in patients affected by schistosomiasis of 4.6% (70,71). PAH in schistosomiasis may be caused by several mechanisms. Development of portal hypertension leading to POPH, occlusion of pulmonary arteries by *Schistosoma* eggs and inflammatory mechanisms have been discussed (72,73).

Treatment of PAH

Treatment of PAH and most of its associated forms is currently based on three main pathways (2). As mentioned in the previous section endothelin-1, a potent vasoconstrictor, is involved in the pathogenesis of pulmonary vascular disease. Accordingly, several substances blocking ET_A receptors or ET_A and ET_B receptors have been studied and approved for the treatment of PAH (74–76). Another pathway used as treatment target is the NO pathway. By inhibiting pulmonary phosphodiesterase 5 (PDE5) or stimulating the soluble guanylate cyclase (sGC) increased cyclic GMP (cGMP) levels are inducing protein kinase G (PKG) mediated vasodilatation (77–79). Another target is prostaglandin I₂ (PGI₂) a potent vasodilator. Anti-thrombotic, anti-proliferative and anti-inflammatory properties were reported.

Prostacyclin analogues (prostanoids) were the first therapies effectively used for PAH. Besides intravenous and subcutaneous application, prostanoids can also be inhaled or orally administered (80–82).

Other therapies for PAH include high dose calcium channel blockers (CCB) as well as experimental approaches using tyrosine kinase inhibitors (TKI). Patients with a significant response to NO during right heart catheterization, defined as a reduction of the mPAP ≥ 10 mmHg with an absolute value of mPAP ≤ 40 mmHg, seem to profit from high-dose CCB treatment. CCB are primarily acting via vasodilatation of pulmonary arteries (83,84). Most recently it has been shown that imatinib a PDGF receptor inhibitor reverses pulmonary vascular remodelling in animal models of PAH with normalization of pulmonary hemodynamics (85). Moreover, it improved symptoms and hemodynamics in patients with severe PAH (86). However, due to an increased risk for subdural hematomas in patients also receiving concomitant anticoagulation, studies evaluating Imatinib have been discontinued due to safety reasons. Nevertheless, TKIs seem to be a promising group of substances targeting pulmonary vascular remodelling.

Treatment of pulmonary hypertension by targeting pulmonary vasculature is only recommended in patients with PAH or CTEPH in the absence of a compromised left ventricle or significant pulmonary comorbidities where pulmonary vasodilatation may lead to left heart decompensation or increased ventilation/perfusion mismatch resulting in severe hypoxemia. However, there are conditions with significant right heart strain and pulmonary vascular involvement when pulmonary vascular therapy may be considered (see chapters below).

2. Pulmonary hypertension and left heart disease

Diseases of the left heart are one of the main causes for PH. The underlying mechanism is an elevation of the left ventricular end-diastolic pressure (LVEDP) leading to pulmonary venous congestion and consequently to an elevation of the pulmonary arterial pressure. The most common conditions causing pulmonary venous congestions are heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF) and valvular heart disease. Thickening of the pulmonary veins and formation of a neo-intima have been

described in patients with PH due to left heart disease. Moreover, in some cases a secondary involvement of pulmonary arteries may occur together with vasoconstriction, media hypertrophy and thickening of pulmonary arteries. This condition has also been described as congestive pulmonary arteriopathy (87,88).

From a hemodynamic point of view, PH in left heart disease is characterised by an elevation of both mPAP and pulmonary arterial wedge pressure (PAWP) (89). Under physiological conditions, PAWP is considered to be close to the LVEDP (mean \pm SD: 8.0 \pm 2.9 mmHg). A PAWP is considered pathological once it exceeds the 2nd standard deviation (14 mmHg). However, for historical reasons a PAWP > 15 mmHg is currently used as cut-off for pulmonary venous hypertension. Dependent on the presence or absence of a significant pulmonary arteriopathy it can be further categorized as combined pre- and postcapillary PH (CpcPH) or as isolated post capillary PH (IpcPH) (Table 2).

Hemodynamic definition of PH in left heart disease	PH	PAWP	PVR
Isolated postcapillary PH (IpcPH)	present	> 15 mmHg	\leq 3 WU
Combined pre- and postcapillary PH (CpcPH)	present	> 15 mmHg	> 3 WU

Table 2: Hemodynamic definition of PH in left heart disease (89); PH: pulmonary hypertension, PAWP: pulmonary arterial wedge pressure, PVR: pulmonary vascular resistance;

Interestingly, the presence of a significant precapillary component by means of an elevation of PVR seems to be an independent predictor of poor outcome in patients with PH due to left heart disease (90,91). This may underline the clinical relevance of pulmonary arterial involvement in this subtype of patients. This observation triggered several attempts to treat patients with CpcPH using pulmonary vasoactive drugs.

Studies evaluating pulmonary vasoactive treatment in the setting of left heart disease led to controversial results with most of the studies not reaching clinically relevant

end points or even causing adverse effects. Therefore, PAH medication is not recommended for patients with PH due to left heart disease and may only be considered in clinical trials for a selected group of patients (2).

3. Pulmonary hypertension and pulmonary disease

Lung diseases are often associated with PH. On the one hand they may be the underlying reason for PH themselves on the other hand they may complicate the course of disease in patients with PAH. In both scenarios the combination of chronic lung disease and PH or PAH is associated with worse functional status and poor outcome.

Multiple pulmonary diseases may result in PH. The highest prevalence has been reported in COPD, idiopathic pulmonary fibrosis (IPF) and combined pulmonary fibrosis and emphysema (CPFE) (92–94). The main pathological feature in COPD and IPF is a loss of functional pulmonary parenchyma, either by development of interstitial fibrosis or by destruction of vital pulmonary tissue and development of emphysema. This may directly lead to a decrease in the number of pulmonary capillaries taking part in the gas exchange. Whether and to which extent pulmonary vascular pruning exists or is contributing to the development of PH-Lung in humans is still matter of debate. Although pulmonary vascular remodelling is present in both PH-IPF and PH-COPD, recent studies revealed profound differences in morphological patterns between both entities of PH-Lung. In contrast to PH-IPF, where uniform reduction of luminal area occurs across vessels of different size, remodelling of pulmonary vessels in COPD was predominantly detected in smaller vessels (95). Vascular remodelling is not exclusively seen in patients with advanced COPD (96,97). It is also present in patients with mild COPD or in smokers with normal lung function who do not suffer from hypoxaemia (98,99). Besides, PH is also seen in conditions such as asthma, sarcoidosis, cystic fibrosis (CF), lymphangioleiomyomatosis (LAM), Langerhans Cell Histiocytosis (LCH) and hypersensitivity pneumonitis (HP) (94,100–103).

In general, chronic lung diseases cause mild or moderate elevation of pulmonary pressure (92,104). Severe PH seems to be uncommon in COPD with only few patients (<5%) exceeding a mPAP more than 40 mmHg (104). In order to define

patient collectives that may profit from pulmonary vasoactive treatment, and to avoid overtreatment of patients with mild to moderate PH-Lung, where adverse effects of vasoactive therapy may outweigh potential benefits, several attempts have been made to define what is “severe” PH-Lung. In the case of severe PH-Lung other possible reasons for hemodynamic impairment such as left heart disease or acute and chronic pulmonary thromboembolic disease have to be ruled out. According to the “Kölner Konsensus Konferenz” held in 2010 in Cologne, 2 of the following 3 criteria should be present in the case of severe PH-Lung: $mPAP > 35\text{mmHg}$, $mPAP \geq 25\text{ mmHg}$ with a cardiac index (CI) $< 2.0\text{ L/min/m}^2$, pulmonary vascular resistance (PVR) $> 6\text{ WE}$ (105). This definition was further adapted by the Nizza working group on PH-Lung in 2013 defining severe PH-Lung as $mPAP > 35\text{mmHg}$ or $mPAP \geq 25\text{ mmHg}$ and $CI < 2.0\text{ ml/min/m}^2$ (106). Finally, according to the recent ESC/ERS guidelines, severe PH lung is defined as $mPAP > 35\text{ mmHg}$ in combination with either a $CI < 2.5\text{ L/min/m}^2$ and/or a $PVR > 3\text{ WU}$ (2). Although there is no strong evidence for one of these definitions, the relevance of significantly elevated PVR in the setting of chronic lung disease has been shown by recent studies (107,108). Another field of uncertainty is the adequate definition of relevant lung disease as cause for PH. This is of special interest as mild obstructive or restrictive ventilatory patterns may also be present in the setting of pulmonary arterial hypertension (PAH) (109,110). Accordingly, there may be a predominant pulmonary condition or a predominant pulmonary vascular disease. Seeger and colleagues made a first attempt in defining relevant pulmonary conditions (106). Their criteria implemented pulmonary functional features ($FEV1 < 60\%$ of predicted, $FVC < 70\%$ of predicted), as well as morphological features based on CT-scans (signs of emphysema and/or fibrosis). The clinical relevance of recommended definitions for different phenotypes of PH-Lung still needs to be investigated. At the world conference in Nice, 2018, a refined algorithm for differentiating PH-Lung and PAH with chronic lung disease has been proposed also incorporating results from cardiopulmonary exercise testing (111) (Table 3).

Characteristics favouring PAH	Tests	Characteristics favouring PH-Lung
Assessment of the extent of lung disease		
Normal or mildly impaired: FEV1 >60% pred (COPD) FVC >70% pred (IPF) Low diffusion capacity in relation to obstructive/restrictive changes	Pulmonary function test	Moderate to very severely impaired: FEV1 <60% pred (COPD) FVC <70% pred (IPF) Diffusion capacity “corresponds” to obstructive/restrictive changes
Absence of or only modest airway or parenchymal abnormalities	High-resolution CT scan	Characteristic airway and/or parenchymal abnormalities
Assessment of pulmonary hemodynamics		
Moderate-to-severe PH	Right heart catheterisation / Echocardiogram	Mild-to-moderate PH
Additional testing		
Present	PAH risk factors (e.g. HIV, connective tissue disease, BMPR2 mutations, etc.)	Absent
Features of exhausted circulatory reserve: Preserved breathing reserve Reduced oxygen pulse Low CO/V'O ₂ slope Mixed venous oxygen saturation at lower limit No change or decrease in P _a CO ₂ during exercise	Cardiopulmonary exercise test (PaCO ₂ particularly relevant in COPD)	Features of exhausted ventilatory reserve: Reduced breathing reserve Normal oxygen pulse Normal CO/V'O ₂ slope Mixed venous oxygen saturation above lower limit Increase in P _a CO ₂ during exercise

Table 3: Proposed criteria from the PH world conference 2018 for differentiating PH-Lung from PAH in the setting of lung disease; adapted from Nathan et al. (111);

Currently, treatment of PH-Lung using PAH drugs is not recommended (112). There may, however, be some exceptions, where the use of pulmonary vasoactive drug could be considered. Patients with severe PH-Lung and/or severe right heart failure should therefore be referred to expert centers and final decision on treatment should be made on an individual basis. Data from retrospective analysis revealed that those patients with severe PH may profit from PAH specific treatment (113–115).

4. Pulmonary hypertension and pulmonary artery obstruction

The most prominent example for PH due to obstruction of the pulmonary arterial system is chronic thromboembolic pulmonary hypertension (CTEPH). It potentially occurs in a subset of patients after recurrent pulmonary embolism (116). The incidence of CTEPH after acute pulmonary embolisms is reported to range from 0.4% to 6.2% (117). Besides, chronic organised thromboembolic occlusion of pulmonary arteries, vascular remodelling and altered angiogenesis seem to be involved in the pathogenesis of CTEPH. In addition, a progressive obstruction of segmental arteries over the course of disease is suspected (118). CTEPH is defined as precapillary pulmonary hypertension (mPAP \geq 25 mmHg, PAWP \leq 15 mmHg and PVR $>$ 3 WU) and the presence of persistent perfusion defects of the lung. Patients not fulfilling the mPAP criterion of 25 mmHg are currently considered to suffer from chronic thromboembolic pulmonary disease (CTED).

Besides a life-long anticoagulation, pulmonary endarterectomy (PEA) is the gold standard for treatment for patients who are technically operable (119). In this regard, 3-year survival rates of 90% were reported. For patients with peripheral chronic thromboembolic disease, where PEA is not possible, pulmonary balloon angioplasty (PBA) could be considered (120). Inoperable patients may benefit from medical treatment targeting pulmonary vasoconstriction. The only approved pulmonary vasoactive treatment for CTEPH is Riociguat a stimulator of the soluble guanylate cyclase (sGC) (121). Moreover, endothelin receptor antagonists, although not approved in this indication, have been shown to improve pulmonary hemodynamics in CTEPH (122).

5. Multifactorial PH

Group 5 represents conditions that cannot be classified by the previous groups or where the underlying mechanisms of PH are only poorly understood. It includes haematological disorders, systemic and metabolic diseases including sickle cell anaemia, beta thalassemia, myeloproliferative disease, splenectomy, sarcoidosis, Langerhans cell histiocytosis, thyroid disease, Morbus Gaucher, tumors and fibrosing mediastinitis. Diagnosis may be difficult and treatment should focus on reversing the underlying condition.

Aims

We aimed to assess the prognostic relevance of mildly elevated mPAP between the established cut-off for pulmonary hypertension (mPAP \geq 25 mmHg) and the normal mPAP + the 1st standard deviation (14.0 + 3.3 mmHg) reported from the literature. We further wanted to assess prognostic cut-offs specific for our collective that are independent from the cut offs-reported in the literature. In a second step we corrected for prognostic baseline characteristics to check whether mildly elevated mPAP is an independent predictor of mortality. We hypothesized that mildly elevated mPAP is an independent predictor of poor prognosis.

H₀: There is no prognostic difference between normal- and mildly elevated mPAP

H₁: There is a prognostic difference between normal- and mildly elevated mPAP

Material and Methods

This study includes both data from a retrospective cohort as well as data from a prospectively enrolled cohort. Data used for this study were gathered during work-up in patients suspected to suffer from pulmonary vascular disease and/or unexplained exertional dyspnea. Furthermore, risk factors and patient characteristics have been assessed.

Patients and ethics

The retrospective and prospective collectives were combined for the final analysis. This study and methods used for data collection and analyses were approved by the ethics committee of the Medical University of Graz (reference number: 23-408ex10/11). Moreover, this study was registered at ClinicalTrials.gov (NCT01607502). The study protocol conformed to the Declaration of Helsinki.

Retrospective collective

Data from patients undergoing RHC between 2005 and 2011 were retrospectively registered at the data collection system of the Ludwig Boltzmann Institute for Lung Vascular Research and the Division of Pulmonology, Department of Internal Medicine of the Medical University of Graz.

Prospective collective

From August 2011 to October 2014, consecutive patients were prospectively enrolled into the registry after signing informed consent.

Screening

Patients included into the study represent a preselected group referred to our centre for further work-up regarding suspected pulmonary vascular disease. Hence patients were initially evaluated using non-invasive tools including ECG, echocardiography, laboratory testing (NTproBNP), pulmonary function testing, chest x-ray and cardiopulmonary exercise tests, focusing on signs and symptoms of early and advanced pulmonary vascular disease (see sections below). The indication for invasive assessment using right heart catheterization (RHC) was made in patients with suspected pulmonary vascular disease and/or otherwise unexplained symptoms based on the guidelines previously published for the screening and diagnosis of pulmonary vascular disease (2). According to recent guidelines, RHC should be considered in patients who are under suspicion of pulmonary arterial hypertension (PAH) where pulmonary vasoactive treatment may be indicated or in patients where chronic thromboembolic hypertension (CTEPH) is suspected and further work-up regarding pulmonary endarterectomy or vasoactive medication is needed. However, it may be also indicated in patients with pulmonary disease with severe pulmonary hypertension. Therefore, patients with pulmonary disease underwent RHC, if there was suspicion for severe concomitant pulmonary hypertension and/or right heart decompensation. In patients with previously diagnosed left heart disease, RHC was performed if normal PAWP was suspected and/or there were signs of severe right heart strain or right heart decompensation, including a severely dilated right atrium and/or a massively enlarged right ventricle. Patients with underlying left heart disease and pulmonary comorbidities without signs of significant right heart strain or significant pulmonary hypertension were not considered for invasive hemodynamic assessment.

Screening Echocardiography

Echocardiography is currently recommended as main screening tool for pulmonary hypertension (2). Therefore, echocardiography was also one of the major factors influencing the indication for RHC in our cohort of patients. The recommended echocardiographic screening algorithm and screening probability for PH is shown in Table 4 (2,15). In patients with detectable tricuspid regurgitation, continuous wave (CW) Doppler sonography may be used to estimate the tricuspid regurgitation velocity (TRV) during systole. According to the simplified Bernoulli equation, TRV can be estimated by the pressure gradient between the right atrium and the right ventricle during systole ($\text{gradient pressure} = 4 * v^2$). By adding an estimation of the right atrial pressure (RAP) the systolic pulmonary arterial pressure can be calculated ($\text{SPAP} = \text{gradient pressure} + \text{RAP}$) (123,124). Right atrial pressure was estimated by assessing the diameter and collapse of the inferior vena cava as previously described (125). However, it is known that sensitivity and specificity of estimated SPAP using echocardiography may be significantly influenced by both patient- as well as operator dependent factors (126–129). Therefore, other echocardiographic signs of right ventricular strain are currently recommended to support the suspicion for pulmonary hypertension (2,15). These supportive criteria for the presence of significant right heart strain are shown in Table 5.

All patients underwent standardized echocardiography for assessment of right ventricular afterload and right ventricular strain prior to RHC. From 2005 to 2012 ultrasound investigation was performed by a Vivid Five GE Vingmed Ultrasound® and a 3.5 MHz phased transducer. Starting with April 2012 a Vivid E9 Ultrasound® with a 4.5 MHz ultrasound probe was used.

Peak TRV m/s (SPAP mmHg)	Other signs of PH	Echocardiographic probability of PH
≤ 2.8 (≤ 36) or not measurable	No	Low
≤ 2.8 (≤ 36) or not measurable	Yes	Intermediate
2.9 – 3.4 (27 - 50)	No	
2.9 – 3.4 (27 - 50)	Yes	High
> 3.4 (> 50)	Not required	

Table 4: Echocardiographic screening algorithm and screening probability for pulmonary hypertension from (2,15)

A: Ventricle	B: Pulmonary artery	C: Inferior vena cava and right atrium
RV/LV basal diameter > 1.0	RV outflow Doppler acceleration time < 105 ms and/or mid-systolic notching	Inferior cava diameter > 21 mm with decreased inspiratory collapse (< 50% with a sniff or < 20% with quiet inspiration)
Flattening of the interventricular septum (LV excentricity index > 1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity > 2.2 m/s	RA area (end systole) > 18 cm ²
Pulmonary artery diameter > 25 mm		
At least signs of two different categories (A/B/C) from the list should be present to alter the echocardiographic probability of PH.		

Table 5: Supportive criteria for pulmonary hypertension from (2,15)

Pulmonary Function Testing

Pulmonary function testing is a major corner stone of PH diagnosis (2). Although it is not used as primary screening tool for PH it is needed to further differentiate PH subtypes. Most frequently, pulmonary functional impairment is found in patients with PH due to restrictive or obstructive lung disease. However, reductions of FVC, FEV1 and/or DLCO may also be seen in patients with PAH, left heart disease, and CTEPH (109,110,130). Therefore, differentiating between PAH and PH due to chronic heart or lung disease may be difficult. Based on expert consensus, different cut-offs for

pulmonary function parameters have been introduced in order to facilitate the differentiation of those phenotypes (2,106) and were also used in our collective to define significant pulmonary comorbidities (see chapter: “Evaluation of Cardiopulmonary Comorbidities”).

Pulmonary function tests including bodyplethysmography and assessment of carbon monoxide diffusion capacity (DLCO) were performed under standard conditions. Spirometry and DLCO measurement were performed using a Master-Screen-PFT/Jaeger[®]. For bodyplethysmography we used a Master-Screen Body/Jaeger[®]. Prior to the measurement age, gender, body weight and body height were collected and saved. Patients were instructed by health care professionals trained in performing pulmonary function tests. Data from pulmonary function testing, bodyplethysmography and DLCO measurement included:

Forced expiratory volume in 1 second (FEV1)

Forced expiratory vital capacity (FVC)

Tiffeneau index (FEV1/FVC)

Vital capacity (VC)

Total lung capacity (TLC)

Residual volume (RV)

Single breathe diffusion capacity of CO adjusted for hemoglobin (DLCOc SB)

Diffusion capacity for CO adjusted for hemoglobin and alveolar volume (DLCOc VA)

Based on absolute values the percent of predicted was calculated for each variable using published data (131).

Assessment of Exercise Performance

To objectively assess the exercise performance in our collectives, six-minute walking test (6MWT) as well as cardiopulmonary exercise testing (CPET) were performed within a few days from invasive hemodynamic assessment. Both test modalities do

not only reflect individual functional exercise capacity but also show correlations with quality of life and are used to guide treatment decisions in pulmonary vascular disease (2). Moreover, they were shown to be of prognostic relevance in patients with pulmonary vascular disease (132–134).

Six-minute walking test

6MWT was performed under standardized conditions according to recent guidelines (135). Cumulative walking distance was documented after 6 minutes. Every 2 minutes the subjective level of exertion was documented using the BORG categorical ratio ranging from 0 (no exertion or dyspnoea) to 10 (maximum exertion or dyspnoea). Besides, heart rate and oxygen saturation were monitored using a fingertip pulse oximeter MD300D/HABEL Medizintechnik® and documented every 2 minutes.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) is the gold standard for the evaluation of exercise performance. Besides evaluation of the individual maximum work load it is also used to check for cardiac-, respiratory and muscular exercise types of limitations. CPET was performed using an ergoline ergoselect 1200/ Bergmann Medizintechnik GmbH® ergometer. Contraindications for CPET at our center are based on previously published guidelines (136).

Patients were placed in semi-reclined position and a nose clip was attached. The patient was instructed to breathe through a mouth piece. After a resting phase of 2 minutes an incremental increase of 25 Watt work load was performed every 2 minutes. The patients were asked to maintain at least 55 to 65 rotations per minute. Patients were monitored using non-invasive blood pressure measurements and ECG. Blood gases were checked at rest, at peak exercise, 3 minutes after exercise termination and 8 minutes after exercise termination. Possible reasons for exercise termination are listed below.

Subjective reasons for exercise termination:

- limited by symptoms

- maximal exertion

Objective reasons for exercise termination:

- ECG: ischemia signs, complex ectopy, second or third degree heart block
- Fall in systolic blood pressure > 20 mmHg
- Hypertension systolic > 250 mmHg, diastolic > 120 mmHg
- Desaturation \leq 80%
- Sudden pallor
- Loss of coordination, mental confusion
- Signs of respiratory failure

Pulmonary functional parameters during exercise were assessed using a mouth piece with a turbine pneumotachygraph. Primary measures of ventilation included:

Tidal volume (VT)

Respiratory rate (RR)

O₂ and CO₂ were measured end-expiratory breath by breath using a gas analyzer connected to the pneumotachygraph chamber. Direct measurements include:

End-tidal PO₂ (PETO₂)

End-tidal PCO₂ (PETCO₂)

Out of the primary measured variables (VT, RR, HR, PETO₂ and PETCO₂) secondary variables were calculated. These included:

Minute ventilation (VE)

Oxygen uptake (VO₂)

Carbon dioxide output (VCO₂)

Oxygen pulse (VO₂/HR)

Deadspace (VD)

Ratio of physiologic dead space to tidal volume (VD/VT)

Oxygen uptake at maximum work load (peakVO₂)

Respiratory equivalents for O₂ and CO₂ (VE/VO₂, VE/VCO₂)

Anaerobic threshold (AT)

Respiratory exchange ratio (RER)

Metabolic equivalent (MET)

Based on published reference values for peakVO₂, VE and HR at peak exercise the percent of predicted were calculated for each variable and later used to identify the main limiting factor.

Invasive assessment of pulmonary hemodynamics

Right heart catheterization is the gold standard of diagnosis of PH. All patients included into the study underwent RHC. RHC was performed as previously described (137). Following local anaesthesia, the left or right sided internal jugular vein was punctured under ultrasound guidance. Thereafter a 7 to 8 french catheter lock was introduced using Seldinger technique. A fluid filled Swan-Ganz catheter (Edwards Life Sciences, Irwin, CA, USA) was inserted via the catheter lock. The catheter balloon was inflated after reaching the superior vena cava. The catheter was further inserted towards the pulmonary artery inflated until reaching wedge position. Insertion was guided by typical pressure tracings. After reaching wedge position the balloon was deflated and the catheter was fixed at this position.

Using liquid filled catheters makes it necessary to define a zero-reference level outside the body to make hemodynamic measurements reproducible. The measured pressure is the difference between the hydrostatic pressure at the zero-reference level outside the body and the catheter tip in the pulmonary artery. Accordingly, changing the zero-reference level may lead to significant changes in pressures (138).

Until 2013 there was no international consensus on which anatomical structure should be used as reference for the placement of the extra thoracic pressure transducer. Consequently, significant differences in hemodynamic measurements between different centres may have been present. Until 2013 the anterior axillar line was used as zero reference level in our centre. Starting with 2013 the mid thoracic frontal plane, representing the level of the left atrium, was chosen as reference level at our centre based on recent literature and international recommendation (138,139), Figure 2.

Hemodynamic pressure tracings were obtained during normal breathing. The average pressure throughout at least three respiratory cycles was documented. Primary hemodynamic measurements included:

- Systolic pulmonary arterial pressure (sPAP)

- Diastolic pulmonary arterial pressure (dPAP)

- Mean pulmonary arterial pressure (mPAP)

- Pulmonary arterial wedge pressure (PAWP)

- Right atrial pressure (RAP)

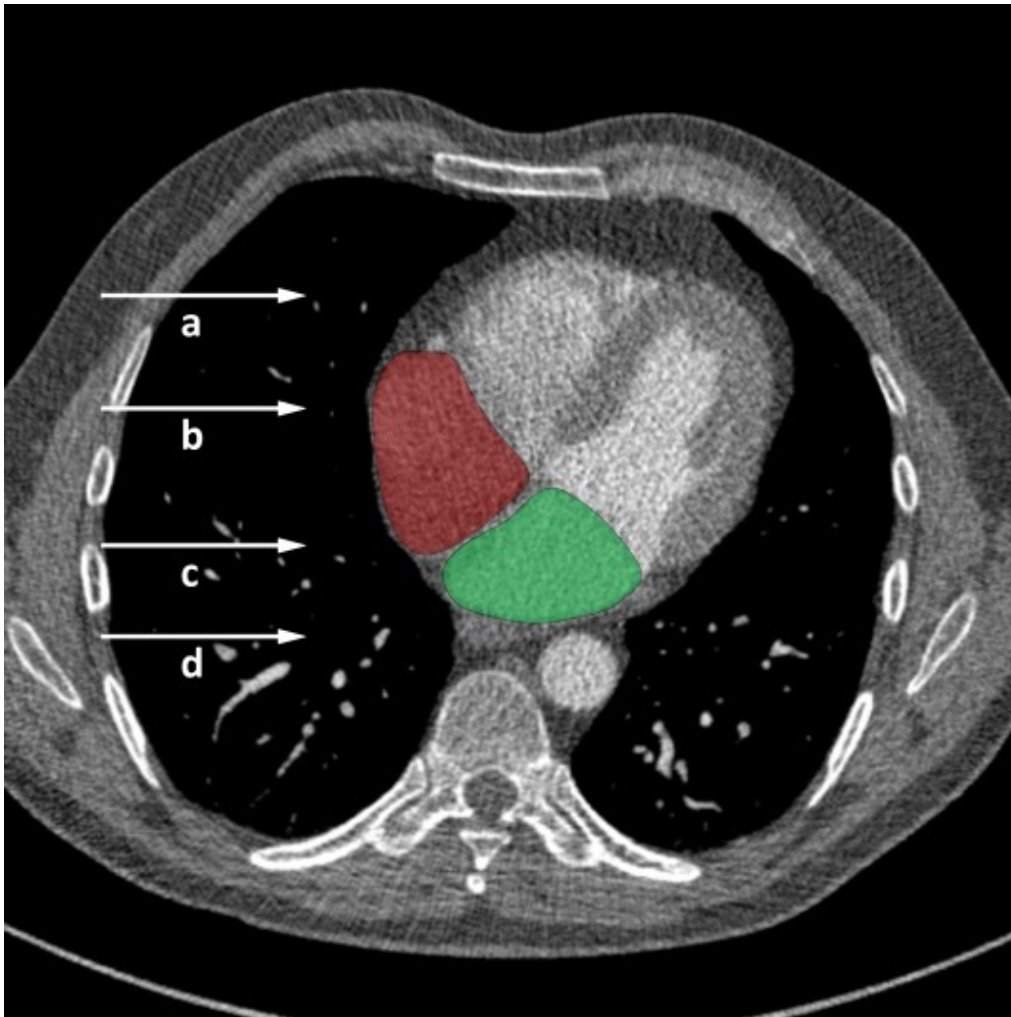


Figure 2: Different reference levels for the placement of the pressure transducer: a 5 cm below sternum, b 1/3 ventral-dorsal distance, c mid thoracic, d 10 cm above table; red area: right atrium; green area: left atrium; starting with 2013 (c) the midthoracic plane was used as zero reference level;

Cardiac output (CO) was directly measured using thermodilution by injecting 10ml of cold 0.9% sodium chloride solution. Calculated secondary hemodynamic variables included:

Cardiac index (CI)

Pulmonary vascular resistance and index (PVR, PVRI)

Systemic vascular resistance and index (SVR, SVRI)

Total pulmonary resistance (TPR)

Blood gas analyses during RHC were performed using an ABL-800-FLEX blood gas analyser (Fa. Drott, Austria). Blood samples were drawn from the central venous- and the pulmonary arterial line as well as from arterialized blood from a hyperaemic ear lobe. Primary measures assessed by blood gas analysis during RHC included:

Arterial partial pressure of oxygen (PaO_2)

Arterial partial pressure of carbon dioxide (PaCO_2)

Concentration of hydrogen protons (PH)

Base excess (BE)

Arterial oxygen saturation (SaO_2)

Mixed venous saturation (SvO_2)

Central venous saturation (ScvO_2)

Secondary blood gas variables included:

Arterial to mixed venous oxygen difference (AVDO_2)

Oxygen uptake (VO_2)

Central venous blood was taken for laboratory testing including assessment of NTproBNP, autoantibody screening, thyroid function, liver function, kidney function and thrombophilia screening.

Based on hemodynamic patterns patients were categorized into: pre- and postcapillary pulmonary hypertension and normal pulmonary pressure ($\text{mPAP} \leq 25$ mmHg) (Table 6). Based on initial hemodynamic pattern patients were further evaluated using lung function testing, chest CT-scans, cardiopulmonary exercise testing, assessment of diffusion capacity of carbon monoxide (DLCO, DLCO/VA) and ventilation perfusion scans. Based on these investigations, patients were classified as PAH (IPAH, HPAH, drug induced PAH, PAH in connective tissue disease, portopulmonary hypertension, PH in congenital heart disease). Pulmonary-veno-occlusive disease, PH due to left heart disease, PH due to lung disease, chronic

thromboembolic disease, PH with unclear or multifactorial mechanisms (see introduction).

Definition:	mPAP	PAWP	PVR
Precapillary pulmonary hypertension	≥ 25 mmHg	≤ 15 mmHg	> 3 WU
Postcapillary pulmonary hypertension	≥ 25 mmHg	> 15 mmHg	>/< 3 WU

Table 6: Previous hemodynamic definition of pulmonary hypertension

Patients not fulfilling criteria for pulmonary hypertension at rest (mPAP < 25 mmHg) were offered to undergo evaluation of pulmonary exercise hemodynamics using a cycle ergometer in supine position. Exercise levels of 25 Watt with increasing workload every 2 min were used and increased until symptom limited exercise termination. At each level mPAP, PAWP, RAP, TPR, PVR and CO were measured. Exercise pulmonary hypertension was defined as mPAP > 30 mmHg and TPR > 3 WU at peak exercise as previously recommended (21).

mPAP groups

For statistical analysis groups needed to be defined based on mPAP. Two different approaches were chosen to define different mPAP cut-offs for statistical comparisons and for the assessment of the prognostic relevance of different mPAP levels.

In our first approach we aimed to assess patients based mPAP cut-offs known from the literature. Accordingly, a normal mPAP was defined as $14.0 + 3.3$ mmHg, corresponding to the physiological mean value (MV) plus the 1st standard deviation (SD). MPAP ≤ 17.3 mmHg was defined as lower normal mPAP. The mPAP range between the MV + 1st SD and the MV + 2nd SD was defined as upper normal mPAP (17.4 – 20.6 mmHg). Borderline mPAP was defined as the range between MV + 2nd

SD and a mPAP of 25 mmHg. Manifest PH was defined based on the recent guidelines as a mPAP \geq 25 mmHg.

In a second approach we aimed to calculate multiple prognostic mPAP cut offs for mortality specific for our collective using a classification and regression tree (CART) analysis. A p-value $<$ 0.05 was considered significant. The minimum number of patients for parent node was set to 100 and the minimum for child node to 50.

Evaluation of cardiopulmonary comorbidities

As mentioned in the introduction, cardiopulmonary comorbidities are major factors influencing pulmonary hemodynamics and therefore, have an essential impact on the final definition of PH as well as on treatment decisions. In order to perform adequate survival analysis, we needed to define clinically relevant cardiopulmonary conditions that may influence the prognosis of our patients. Functional cut-offs for relevant pulmonary comorbidities were based on recent recommendations on how to define restrictive and obstructive conditions in the setting of PVD (2,106). Finally, 9 conditions were defined and included into our analysis (Table 7).

Comorbidity:	Definition:
Coronary heart disease	significant coronary stenosis in at least one major coronary branch based on coronary angiography or history of myocardial infarction
Valvular heart disease	presence of any moderate or severe valve disease (except tricuspid regurgitation)
Systemic hypertension	systolic systemic blood pressure $>$ 140 mmHg or long-term treatment with antihypertensive drugs
Chronic left heart failure	ejection fraction $<$ 50% or diastolic dysfunction $>$ grade II
Atrial fibrillation	persistent or intermittent atrial fibrillation documented by ECG
Pacemaker	presence of cardiac pacemaker
Relevant obstructive lung disease	FEV1/FVC $<$ 70% and FEV1 $<$ 60% of predicted
Relevant restrictive lung disease	TLC $<$ 70% and FVC $<$ 70% of predicted
Sleep apnoea	AHI $>$ 10 verified by polysomnography

Table 7: Definition of cardiopulmonary comorbidities, FEV1: forced expiratory volume in the first second, FVC: forced vital capacity, TLC: total lung capacity, AHI: Apnea Hypopnea

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Data management and statistics

Data from the retrospective collective and prospective collective were entered into our databank (research documentation and analysis: RDA). After end of data entry, data were imported into our statistical programs.

Data are represented as means value (MV) \pm standard deviation (SD) or median value and interquartile range (IQR) for continuous variables. Absolute values and relative frequencies are used to express categorical data. Group comparisons were performed using the Kruskal Wallis test for non-parametric continuous or ordinary scaled variables. One-way ANOVA was used for parametric continuous variables. Categorical data were compared using cross tables and chi-square tests. Patients were grouped according to their baseline mPAP values. Literature based mPAP groups, as well as mPAP groups calculated from our unbiased approach based on CART analysis were used separately for survival analysis. Survival data including date of death and cause of death were obtained from the federal Austrian institute for statistics (Statistik Austria, Guglgasse 13, 1110 Vienna, Austria). Univariate survival analysis using Kaplan-Meier curves and log-rank tests were performed to analyze the impact of mPAP stages (lower-normal, upper-normal, borderline pressure, PH) on overall survival (time from RHC to death). A multivariate Cox regression model including mPAP, number of cardiopulmonary comorbidities and age was used. Statistical analysis was performed using IBM SPSS Statistics (Release 20.0.0. 2011. Chicago (IL), USA: SPSS Inc., an IBM Company) software.

Results

Patient characteristics

Overall 547 patients were included into the study. The majority of patients were female (64%). Mean age was 62 years. All patients underwent RHC. Our retrospective collective included 394 patients (72%) undergoing RHC between 2005 and 2011. 153 patients (26%) were prospectively recruited between August 2011 to October 2014. Patients within the prospective cohort had significantly higher BMI, higher PAWP and RAP. Moreover, FVC and TLC were significantly lower in the prospective cohort. Besides these differences, there were no significant differences between the prospective and retrospective collective (Table 8). 290 patients fulfilled criteria for pulmonary hypertension (mPAP \geq 25 mmHg). Out of these, 74 patients (26%) were diagnosed as PAH with 79% of them being treated with at least one pulmonary vasoactive drug during the observation period. The diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) was made in 53 patients (18%) with 74% of them being treated with pulmonary vasoactive medication. Decision on treatment was made on an individual basis dependent on patient characteristics. Therefore, 21 patients with precapillary pulmonary hypertension fulfilling PAH criteria were not considered eligible for PAH treatment. Conditions and reasons for not treating these patients were: hyperdynamic circulatory state in the setting of liver cirrhosis with mild PVR elevation, congenital heart disease without signs of right heart failure, frailty or patient refusal. Out of the remaining 257 patients who did not meet the criteria for PH, 10 scleroderma patients received PAH medication for treatment of digital ulcers. None of the remaining patients received PAH medication. The frequencies of different PH types are listed in Table 9.

Parameters		Retrospective N = 394	Prospective N = 153	p-value
Age (yr)		65 (53 - 71)	66 (54 - 73)	n.s.
Height (cm)		166 (161 - 173)	167 (161 - 175)	n.s.
Weight (kg)		72 (63 - 83)	76 (64 - 90)	0.017
BMI (kg/m ²)		25.9 (22.7 - 29.4)	27.2 (23.8 - 31.5)	0.012
Mean PAP (mmHg)		26 (17 - 39)	29 (18 - 42)	n.s.
PAWP (mmHg)		8 (6 - 11)	10 (7 - 14)	< 0.001
RAP (mmHg)		5 (3 - 8)	6 (5 - 11)	< 0.001
CO (l/min)		4.7 (3.9 - 5.5)	4.5 (3.7 - 5.4)	n.s.
PVR (WU)		3.0 (1.8 - 6.5)	3.3 (1.8 - 7.0)	n.s.
Sex	Female	262 (67%)	88 (58%)	n.s.
	Male	132 (33%)	65 (42%)	n.s.
art SO ₂ (%)		95 (93 - 97)	95 (94 - 96)	n.s.
art pO ₂ mmHg)		68 (60 - 76)	67 (61 - 74)	n.s.
art pCO ₂ (mmHg)		36 (33 - 39)	36 (33 - 39)	n.s.
NT-proBNP (pg/ml)		539 (159 - 1728)	1020 (194 - 2333)	n.s.
FEV1 (%predicted)		79 (61 - 92)	83 (62 - 97)	n.s.
FEV1/FVC (%predicted)		78 (72 - 83)	76 (70 - 79)	0.010
FVC (%predicted)		80 ± 21	87 ± 22	0.002
TLC (%predicted)		107 ± 24	92 ± 18	< 0.001
DLCOcSB (%predicted)		74 ± 22	70 ± 24	n.s.
DLCOcVA (%predicted)		82 (70 - 96)	84 (64 - 99)	n.s.
6 MWD (m)		371 (284 - 441)	383 (279 - 441)	n.s.
PeakVO ₂ (%predicted)		67 (53 - 83)	62 (44 - 81)	n.s.
Comorbidities*	Pulmonary	1.29 ± 1.21	1.13 ± 1.02	n.s.
	Cardiac	0.97 ± 0.91	0.84 ± 0.84	n.s.
	Total Number	0.32 ± 0.56	0.29 ± 0.49	n.s.

Table 8: Patient characteristics; Normally distributed variables are expressed as mean ± SD, non-normally distributed variables are expressed as median and IQR; *expressed as mean ± SD although non-parametric; n.s.: non significant, BMI: body mass index, PAP: pulmonary arterial pressure, PAWP: pulmonary artery wedge pressure, RAP: right atrial pressure, CO: cardiac output, PVR: pulmonary vascular resistance, art SO₂: arterial oxygen saturation, NT-proBNP: N terminal pro brain natriuretic peptide, FEV1: forced expiratory volume in the first second, FVC: forced vital capacity, TLC: total lung capacity, DLCOcVA: diffusion capacity for carbon monoxide corrected for alveolar volume, DLCOcSB: single breath diffusion capacity for carbon monoxide, 6MWD: six minute walk distance, peakVO₂: peak oxygen uptake; from (1); Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society.

PH Classification	No. (%)
PAH:	74 (26%)
IPAH	33 (45%)
HPAH	1 (1.0%)
Drug induced PAH	1 (1.0%)
PAH in connective tissue disease	13 (18%)
Portopulmonary hypertension	8 (11%)
Congenital heart disease	17 (23%)
PVOD	1 (1%)
PH due to left heart disease	59 (20%)
PH due to lung disease	77 (27%)
CTEPH	53 (18%)
PH with unclear/multifactorial mechanisms	27 (9%)

Table 9: Clinical classification of PH patients; PAH: pulmonary arterial hypertension; IPAH idiopathic pulmonary arterial hypertension; HPAH: hereditary pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; CTEPH: chronic thromboembolic pulmonary hypertension; from (1); Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society.

Clinical characteristics of patients with mild changes in pulmonary hemodynamics

There were significant differences between baseline characteristics dependent on the mPAP groups (Table 10). Baseline characteristics such as age, NTproBNP showed a significant increase across the different meanPAP groups with lowest values in the lower normal mPAP groups and highest values within the manifest PH group. Patients within the upper-normal and borderline mPAP groups showed an intermediate increase of age and NT-proBNP. The same pattern was present regarding the number of cardiopulmonary comorbidities. Patients with upper-normal and borderline mPAP had significantly higher numbers of comorbidities as compared to patients with lower normal mPAP. In contrast, markers of exercise tolerance such as six-minute walking distance (6MWD) and percent predicted of peak oxygen uptake

during exercise (peakVO₂) showed a significant decline with increasing mPAP. Patients within the upper normal and borderline mPAP groups had significantly lower 6MWD and peak VO₂ percent predicted as compared to the lower-normal mPAP group (Table 11 and Figures 3 and 4).

Parameters	Lower-Normal (N = 137)	Upper-Normal (N=56)	Bordeline mPAP (N=64)	PH (N = 290)	p-value
Age (yr)	56 (45 - 66)	64 (55 - 72)	67 (58 - 75)	68 (58 - 74)	< 0.001
Height (cm)	167 (160 - 173)	165 (161 - 171)	164 (162 - 169)	167 (161 - 175)	0.027
Weight (kg)	70 (60 - 80)	76 (66 - 85)	72 (63 - 91)	75 (64 - 86)	0.191
BMI (kg/m ²)	25.1 (22.5 - 28.1)	27.2 (24.0 - 30.6)	26.7 (22.9 - 31.2)	26.3 (22.9 - 30.9)	0.009
Ever smoked (%)	56%	55%	50%	54%	n.s.
Sex	Female	42 (75%)	45 (70%)	165 (57%)	0.003
	Male	39 (28%)	14 (25%)	125 (43%)	0.003
art SO ₂ (%)	97 (95- 98)	95 (94 - 96)	95 (93 - 96)	94 (91 - 96)	< 0.001
art pO ₂ mmHg)	76 (71- 83)	70 (63 - 74)	68 (61 - 73)	62 (57 - 70)	< 0.001
art pCO ₂ (mmHg)	36 (34- 38)	36 (33 - 38)	36 (34 - 39)	36 (32 - 41)	0.778
NT-proBNP (pg/ml)	106 (56 - 183)	240 (112 - 551)	444 (219 - 842)	1413 (460 - 3105)	< 0.001
FEV1 (%predicted)	92 (79- 102)	85 (71 - 97)	83 (60 - 92)	70 (55 - 86)	< 0.001
FEV1/FVC (%)	79(76 - 83)	79 (73- 84)	78 (73 - 81)	75 (67 - 81)	< 0.001
FVC (%predicted)	96 (84 - 105)	88 (79 - 100)	83 (60 - 92)	77 (62 - 90)	< 0.001
TLC (%predicted)	106 (93 - 121)	105 (92 - 119)	104 (88 - 116)	97 (85 - 112)	0.004
DLCOcSB (%predicted)	83 ± 18	83 ± 23	71 ± 19	65 ± 23	< 0.001
DLCOcVA (%predicted)	87 ± 17	89 ± 21	83 ± 20	78 ± 27	0.008
Comorbidities*	Pulmonary	0.06 ± 0.24	0.16 ± 0.37	0.31 ± 0.47	0.43 ± 0.59
	Cardiac	0.53 ± 0.64	0.75 ± 0.72	0.94 ± 0.85	1.06 ± 0.93
	Total Number	0.58 ± 0.68	0.91 ± 0.79	1.25 ± 0.91	1.49 ± 1.17

Table 10: Patient characteristics and mPAP; Normally distributed variables are expressed as mean ± SD, non-normally distributed variables are expressed as median and IQR; *expressed as mean ± SD although non-parametric; BMI: body mass index, PAP: pulmonary arterial pressure, PAWP: pulmonary artery wedge pressure, RAP: right atrial pressure, CO: cardiac output, PVR: pulmonary vascular resistance, PH: pulmonary hypertension, art SO₂: arterial oxygen saturation, NT-proBNP: N-terminal pro brain natriuretic peptide, FEV1: forced expiratory volume in the first second, FVC: forced vital capacity, TLC: total lung capacity, DLCOcVA: diffusion capacity for carbon monoxide corrected for alveolar volume, DLCOcSB: single breath diffusion capacity for carbon monoxide;

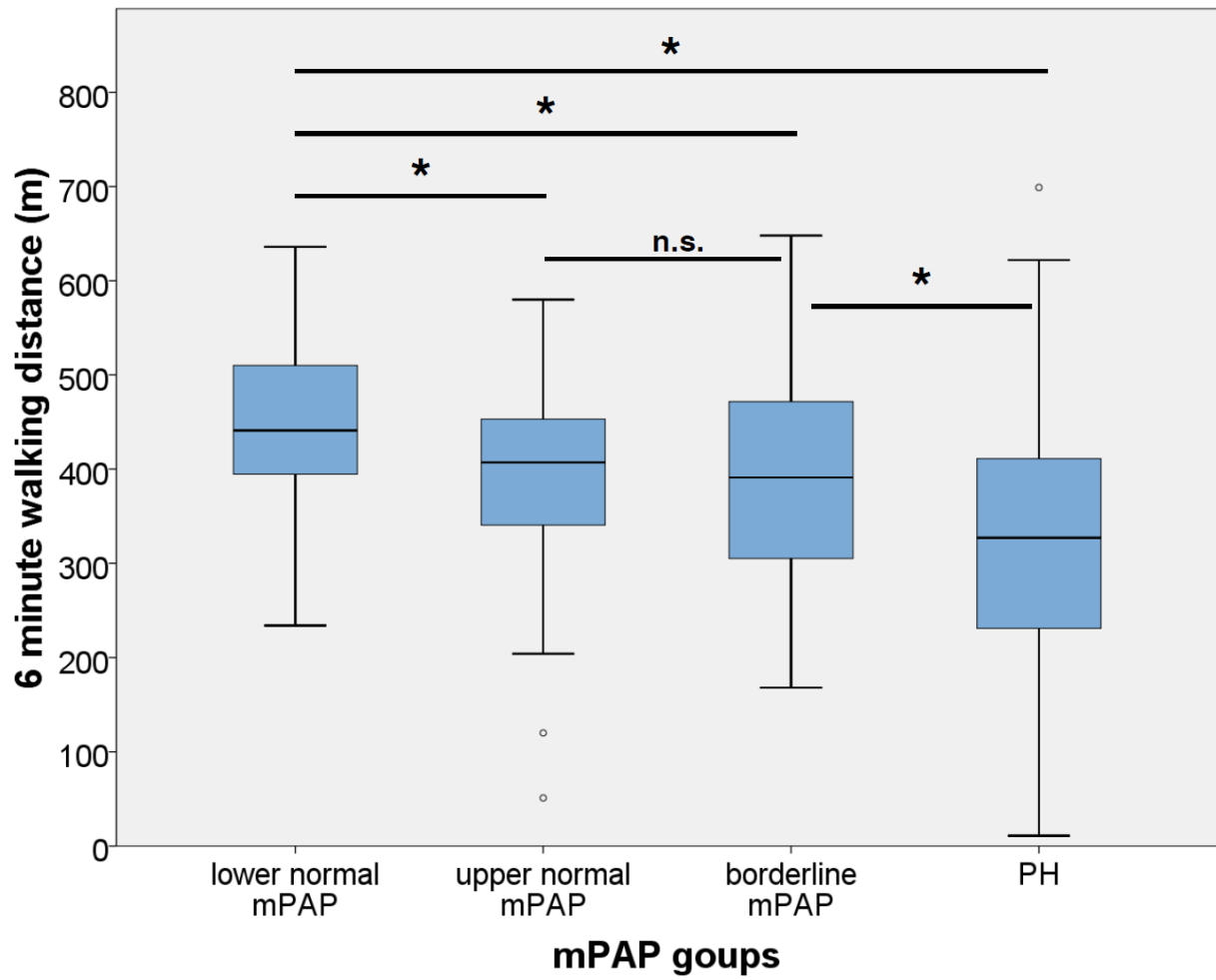


Figure 3: 6-minute walking distance by mPAP groups; *p < 0.05; n.s.: non significant; from (1); Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society.

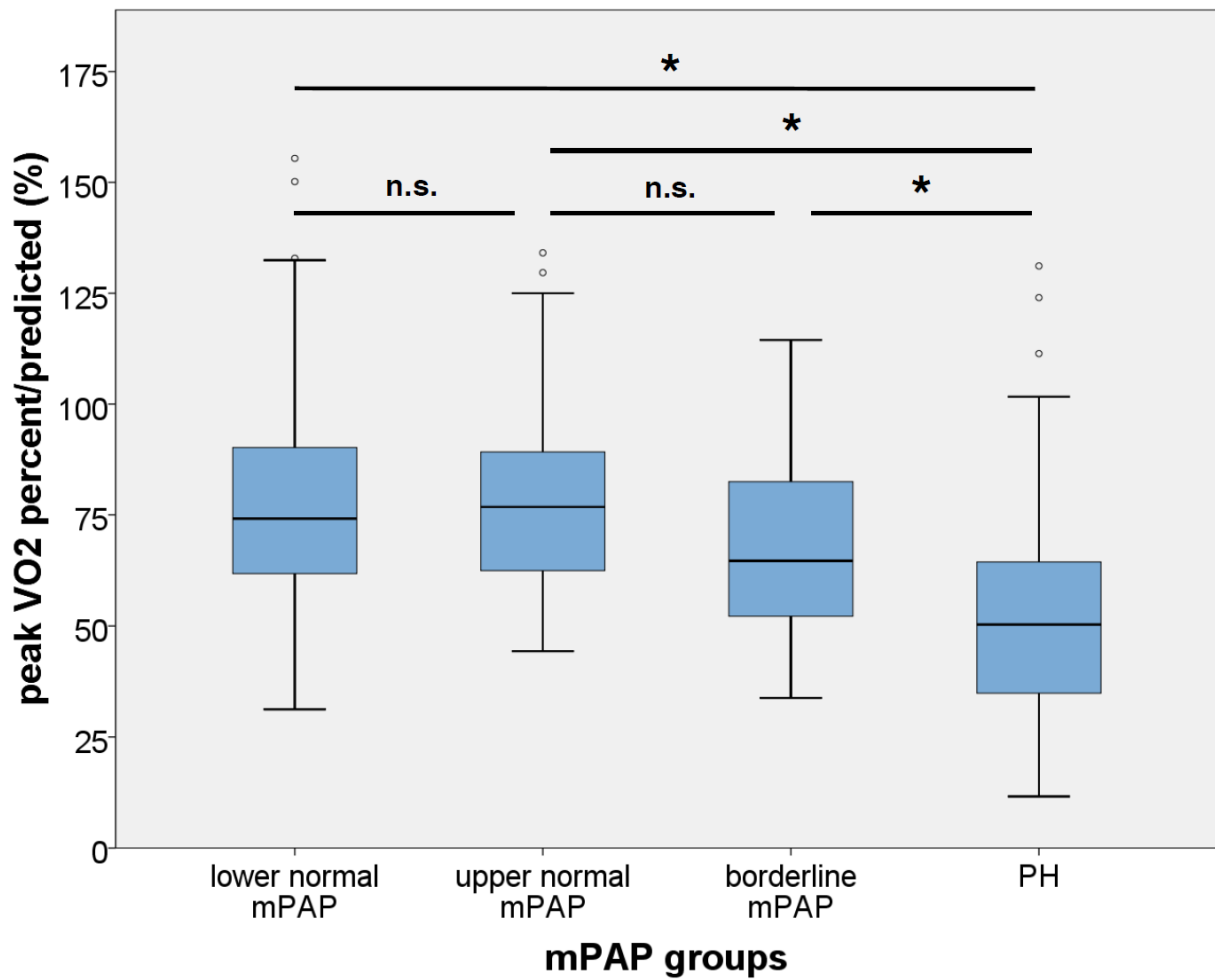


Figure 4: peakVO₂ by mPAP groups; *p < 0.05; n.s.: non significant; from (1); Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society.

Variable:	Lower Normal (N = 137)	Upper Normal (N=56)	Bordeline mPAP (N=64)	PH (N = 290)	p-value
6 MWD (m)	441 (395 - 510)	407 (341 - 453)	379 ± 117	327 (231 - 411)	< 0.001
PeakVO ₂ (%predicted)	78.2 ± 24.6	79.8 ± 21.9	70.5 ± 32.2	52.5 ± 23.7	< 0.001

Table 11: Exercise tolerance and mPAP: Normally distributed variables are expressed as mean ± SD, non-normally distributed variables are expressed as median and IQR; 6MWD: six minute walk distance, peakVO₂: peak oxygen uptake;

Pulmonary hemodynamics at rest

Both PAWP and PVR significantly increased from the lower normal mPAP group towards the manifest PH group, with subclinical but significant increases being present between the upper normal and borderline mPAP groups (Table 12). Moreover, the proportion of patients with PVR > 3 WU was significantly higher in patients with upper-normal and borderline mPAP, steadily increasing towards and reaching its peak in the manifest PH group (Figure 5). However, it never reached 100%. Cardiac output (CO) was lowest in PH patients. No significant differences in CO could be observed between the upper-normal-, borderline mPAP group and the lower normal mPAP group.

Variable:	Lower Normal (N = 137)	Upper Normal (N=56)	Bordeline- mPAP (N=64)	PH (N = 290)	p-value
Mean PAP (mmHg)	14 (12 - 16)	19 (18 - 20)	22 (21 - 23)	39 (31 - 48)	-
PAWP (mmHg)	6 (5 - 8)	10 (7 - 12)	10 (7 - 12)	10 (7 - 15)	< 0.001
RAP (mmHg)	4 (3 - 6)	5 (4 - 7)	6 (3 - 8)	5 (5 - 12)	< 0.001
CO (l/min)	4.8 (4.1 - 5.9)	5.1 (4.2 - 6.2)	4.9 (4.0 - 5.5)	4.5 (3.5 - 5.3)	< 0.001
CI (l/min/m²)	2.7 (2.4 - 3.2)	2.7 (2.3 - 3.2)	2.6 (2.2 - 3.1)	2.4 (2.0 - 2.8)	< 0.001
PVR (WU)	1.45 (1.10 - 1.93)	1.89 (1.35 - 2.55)	2.68 (1.89 - 3.33)	6.09 (3.71 - 9.92)	< 0.001
PVR>3WU N (%)	1 (0.7%)	6 (11%)	23 (36%)	241 (84%)	< 0.001

Table 12: Pulmonary hemodynamics; Normally distributed variables are expressed as mean \pm SD, non-normally distributed variables are expressed as median and IQR; PAP: pulmonary arterial pressure, PAWP: pulmonary artery wedge pressure, RAP: right atrial pressure, CO: cardiac output, CI: cardiac index, PVR: pulmonary vascular resistance, PH: pulmonary hypertension;

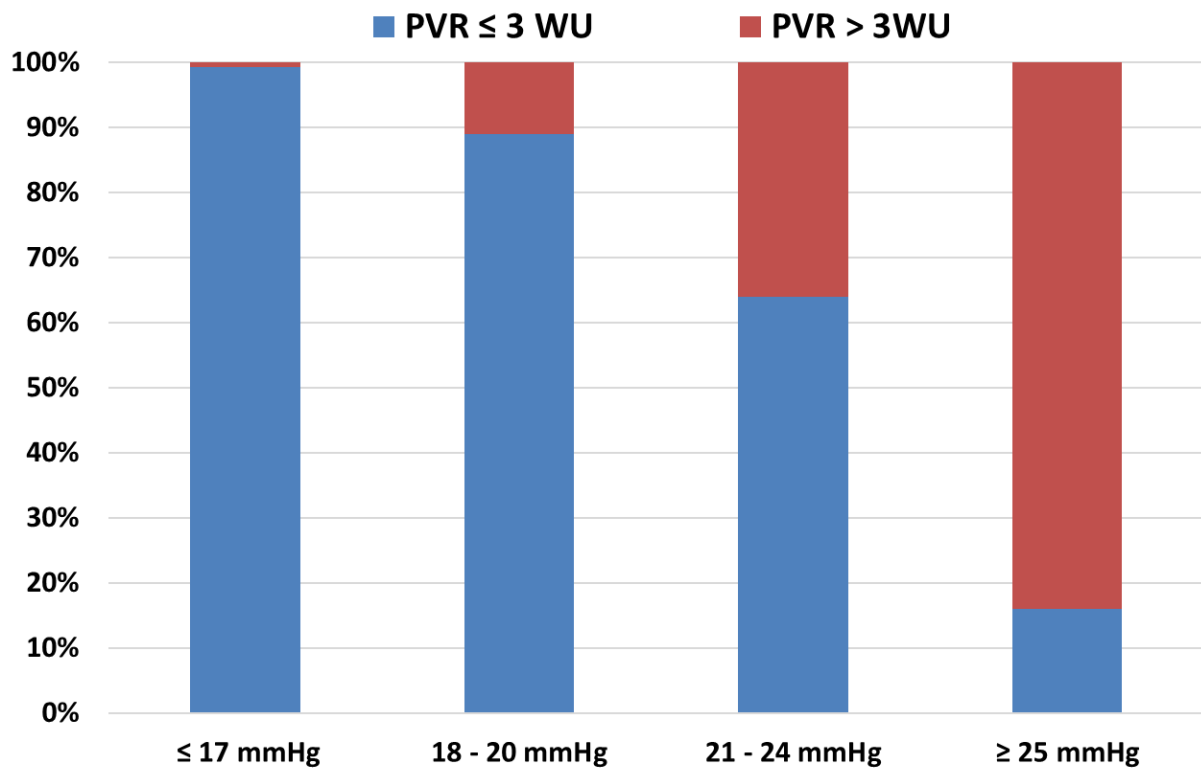


Figure 5: Frequency of PVR > 3 WU dependent on resting mPAP; PVR: pulmonary vascular resistance;

Pulmonary hemodynamics during exercise

N = 206 patients (lower normal mPAP: N = 115, upper normal mPAP: N =44, borderline mPAP: N = 47) underwent exercise RHC. Significant differences in pulmonary hemodynamics during peak exercise were detected between the different mPAP groups (Table 13). MPAP at peak exercise was significantly higher in the upper-normal and borderline mPAP groups as compared to lower normal subjects. The same pattern was present in PAWP, PVR and TPR at peak exercise. In contrast to this, a steady and significant decline in peak cardiac output from the lower normal mPAP group to the borderline mPAP group was observed. N = 120 (58%) patients fulfilled criteria for pathological pulmonary exercise hemodynamics (mPAP at peak exercise > 30 mmHg and TPR at peak exercise > 3 WU) (Figure 6). The proportion of patients fulfilling the current definition for exercise PH was significantly higher within the upper-normal and borderline mPAP groups as compared to the lower normal mPAP group (Figure 7).

Variable:	Lower Normal (N = 115)	Upper Normal (N=44)	Bordeline-mPAP (N=47)	p-value
Mean PAP max (mmHg)	34 ± 10	43 ± 8	46 ± 8	< 0.001
PAWP max (mmHg)	19 ± 7	23 ± 8	23 ± 8	< 0.001
RAP max (mmHg)	9 (7 - 12)	13 (9 - 16)	17 (9 - 20)	< 0.001
CO max (l/min)	11.4 (9.6 – 14.4)	10.7 (7.3 – 13.7)	8.8 (6.8 – 11.7)	< 0.001
CI max (l/min/m²)	6.6 ± 1.6	5.9 ± 1.9	5.1 ± 1.7	< 0.001
PVR max (WU)	1.24 (0.89 - 1.77)	1.70 (1.32 – 2.83)	2.66 (1.84 - 3.47)	< 0.001
TPR max (WU)	2.89 (2.20 – 3.87)	3.90 (2.98 – 6.05)	5.01 (4.23 – 6.95)	< 0.001
EPH N (%)	46 (40%)	32 (73%)	42 (89%)	< 0.001

Table 13: Exercise hemodynamics: Normally distributed variables are expressed as mean ± SD, non-normally distributed variables are expressed as median and IQR; PAP: pulmonary

arterial pressure, PAWP: pulmonary artery wedge pressure, RAP: right atrial pressure, CO: cardiac output, CI: cardiac index, PVR: pulmonary vascular resistance, TPR: total pulmonary resistance;

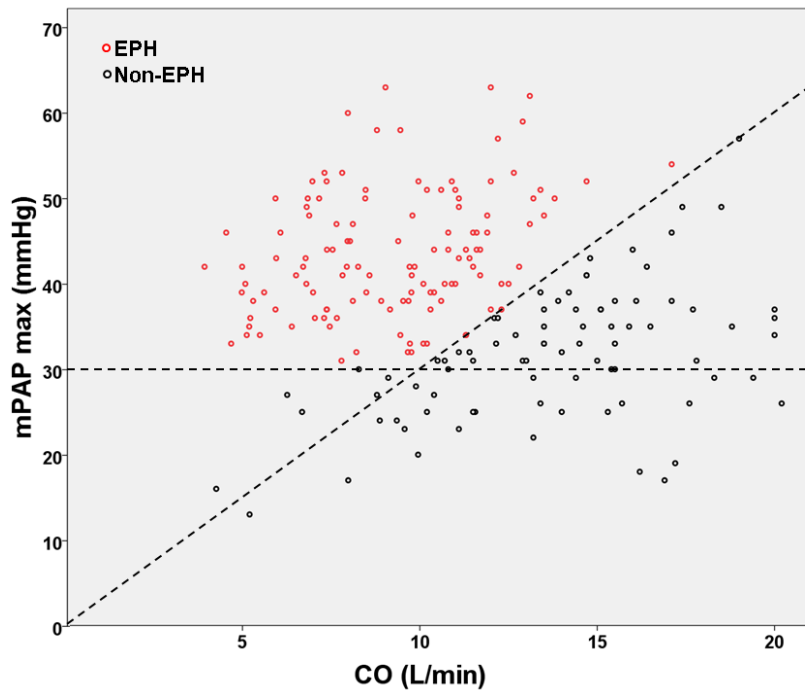


Figure 6: mPAP / cardiac output plots of patients undergoing exercise hemodynamic assessment

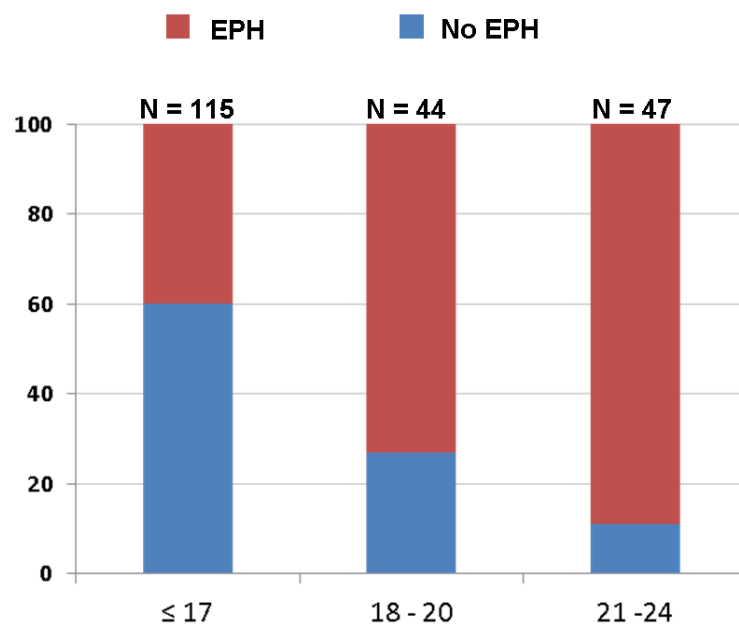


Figure 7: Frequency of exercise PH dependent on resting mPAP; EPH: exercise PH;

All-cause mortality

The median time of follow-up was 45.9 months (IQR: 21.8 – 77.2 months). Within this time, 161 (29%) events occurred. The leading causes of death were cardiovascular disease (n=53 (33%)) respiratory disease (n=26 (16%)) and cancer (n=26 (16%)). All-cause mortality was significantly higher in patients diagnosed with PH. Five-year survival rates were 84% and 58% for non-PH and PH patients (Figure 8).

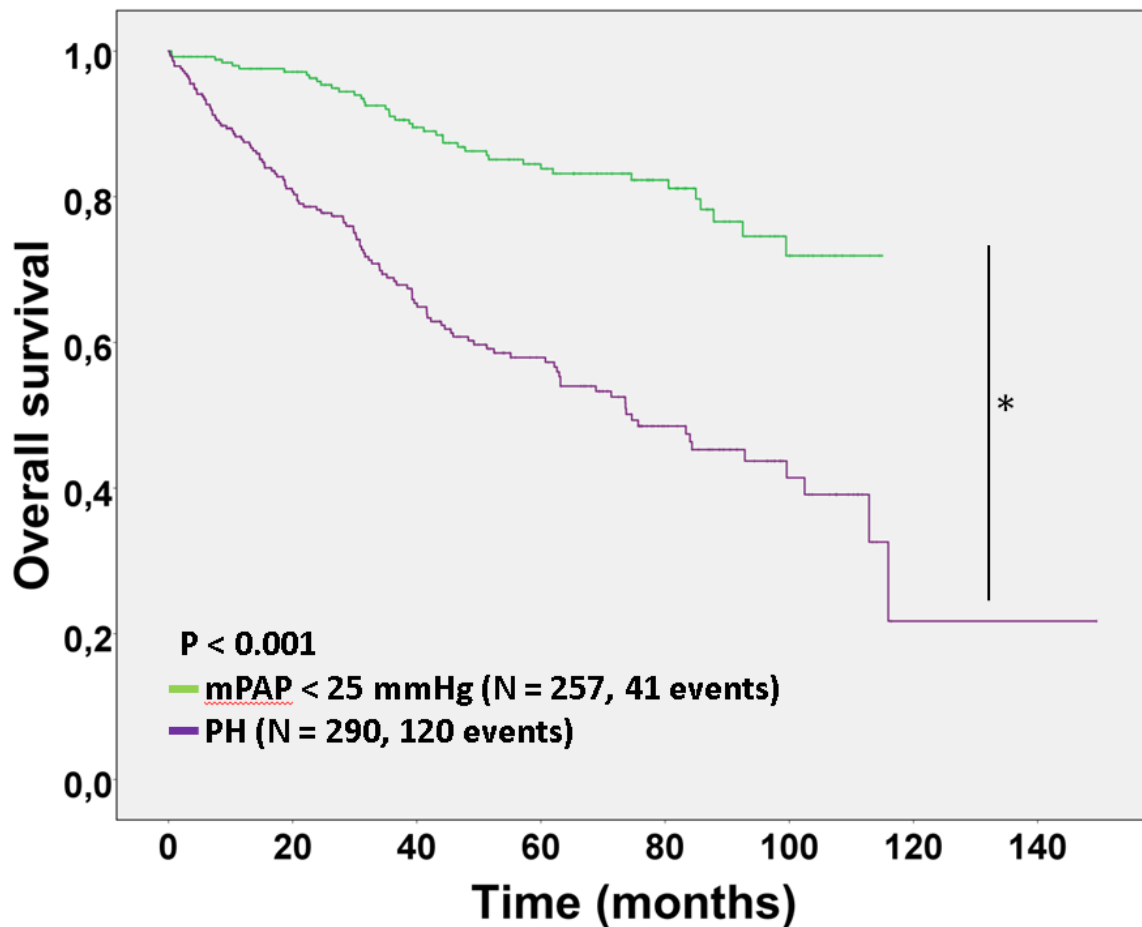


Figure 8: Univariate Kaplan Meier survival analysis in PH and non-PH patients; * p < 0.001;

Survival analysis based on preset-free cut offs

Based on our preset-free regression tree analysis (tree-CART) using mPAP as marker for prognosis, three mPAP groups of significantly different prognosis were identified. The first cut-off point was found at 16.5 mmHg and the second mPAP cut off was found at 26.5 mmHg. Five-year survival rates for these 3 groups were 92%,

77% and 56%, respectively. The mortality risk differed significantly between all three groups with a 3-fold risk elevation being present between the group with the lowest mPAP values and the intermediate mPAP group [HR: 2.76, 95% CI: 1.37 - 5.58 ($p = 0.005$)]. A 7-fold increase of mortality risk was present between the lower mPAP group and patients within the highest mPAP measures [HR: 7.30, 95% CI: 3.82 - 13.93 ($p < 0.001$)]. Kaplan Maier Curves based on cut-offs from Tree Cart analysis are shown in Figure 9.

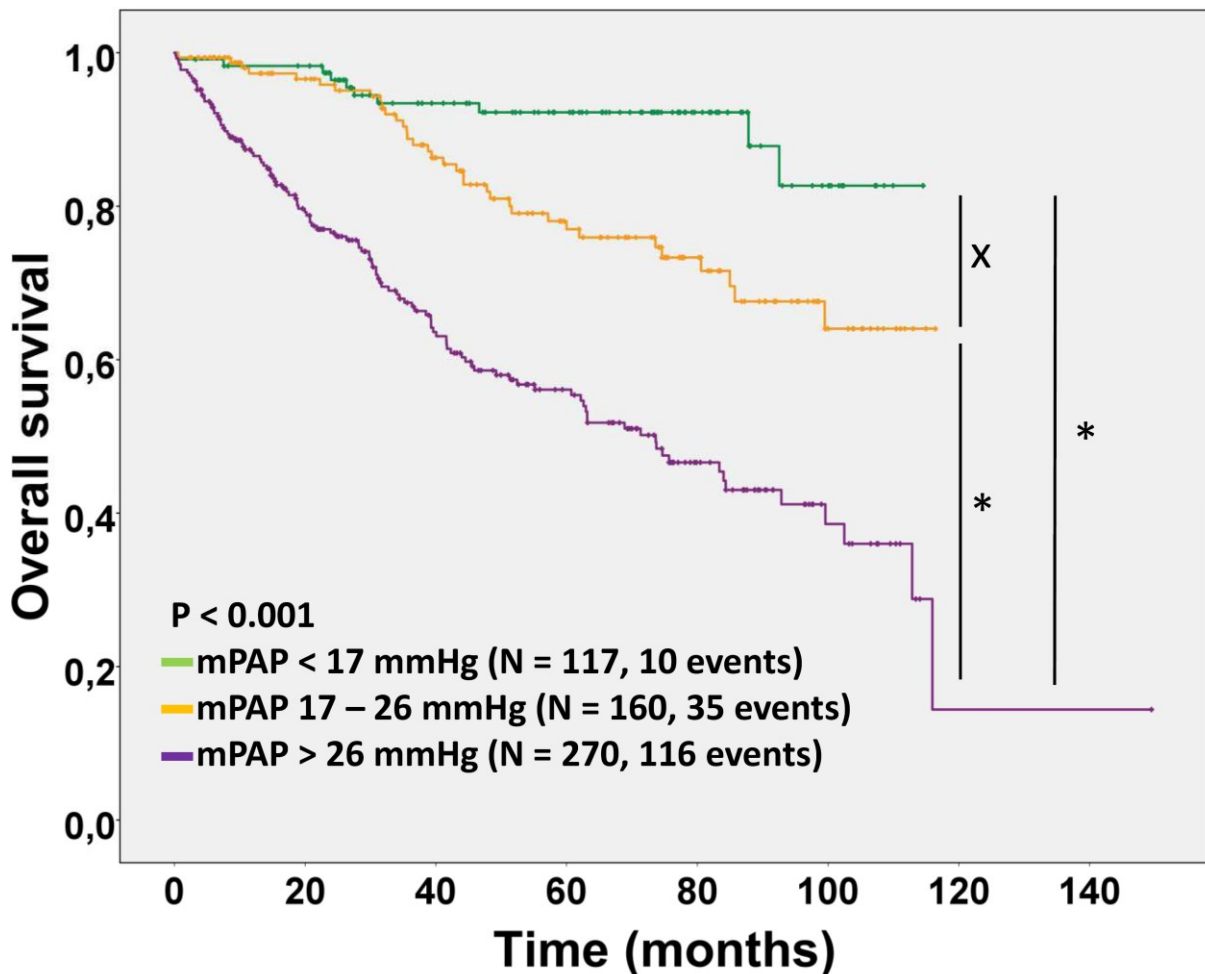


Figure 9: Univariate Kaplan Meier survival analysis based on mPAP groups from preset-free CART analysis; * $p < 0.001$; X $p = 0.003$; from (1); Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society.

Univariate survival analysis based on preset-based cut-offs

Applying cut-offs from the literature revealed five-year survival rates of 92%, 79%, 71%, and 58% in the lower-normal, upper-normal, borderline, and PH groups,

respectively. Univariate survival analysis showed significant differences in all-cause mortality between both the upper-normal and the borderline mPAP groups as compared to the lower-normal mPAP group [HR: 2.37, 95% CI: 1.06 - 5.30 ($p = 0.035$) and HR: 3.20, 95% CI: 1.56 - 6.60 ($p = 0.002$)]. Kaplan Maier Curves based on preset cut-offs are shown in Figure 10.

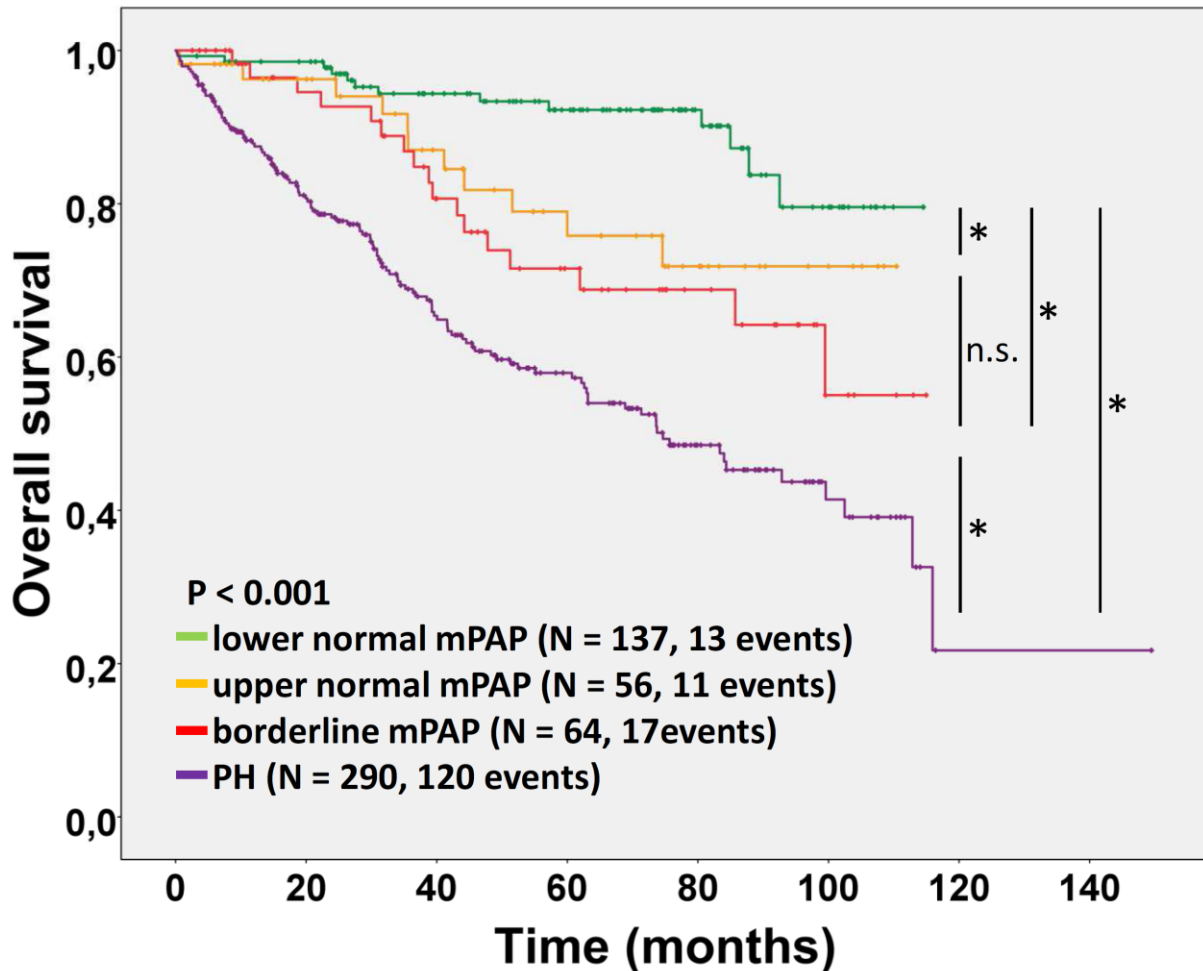


Figure 10: Univariate Kaplan Meier analysis for overall survival in patients of different mPAP groups; * $p < 0.05$; n.s.: non-significant; from (1); Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society.

Multivariate survival analysis based on preset cut-offs

In our multivariate model, including age, number of comorbidities and mPAP groups, mPAP ($p < 0.001$) and age ($p < 0.001$) were independent predictors of overall survival, whereas the number of comorbidities was not significant. A steady decline of all-cause mortality across the different mPAP groups was observed again with the

lowest mortality in the lower normal mPAP group ($p < 0.001$). After multivariate correction the difference between the lower-normal and the upper-normal mPAP groups did not meet statistical significance. However, the contrast between borderline mPAP elevation and lower normal mPAP remained significant [upper normal mPAP: HR: 1.92, 95% CI: 0.85 – 4.289 ($p = 0.115$); borderline mPAP: HR: 2.22, 95% CI: 1.06 – 4.62 ($p = 0.034$); manifest PH: HR: 4.59, 95% CI: 2.56 -8.23 ($p < 0.001$)]. Multivariate COX-Regression analysis based on preset cut-offs is shown in Figure 11.

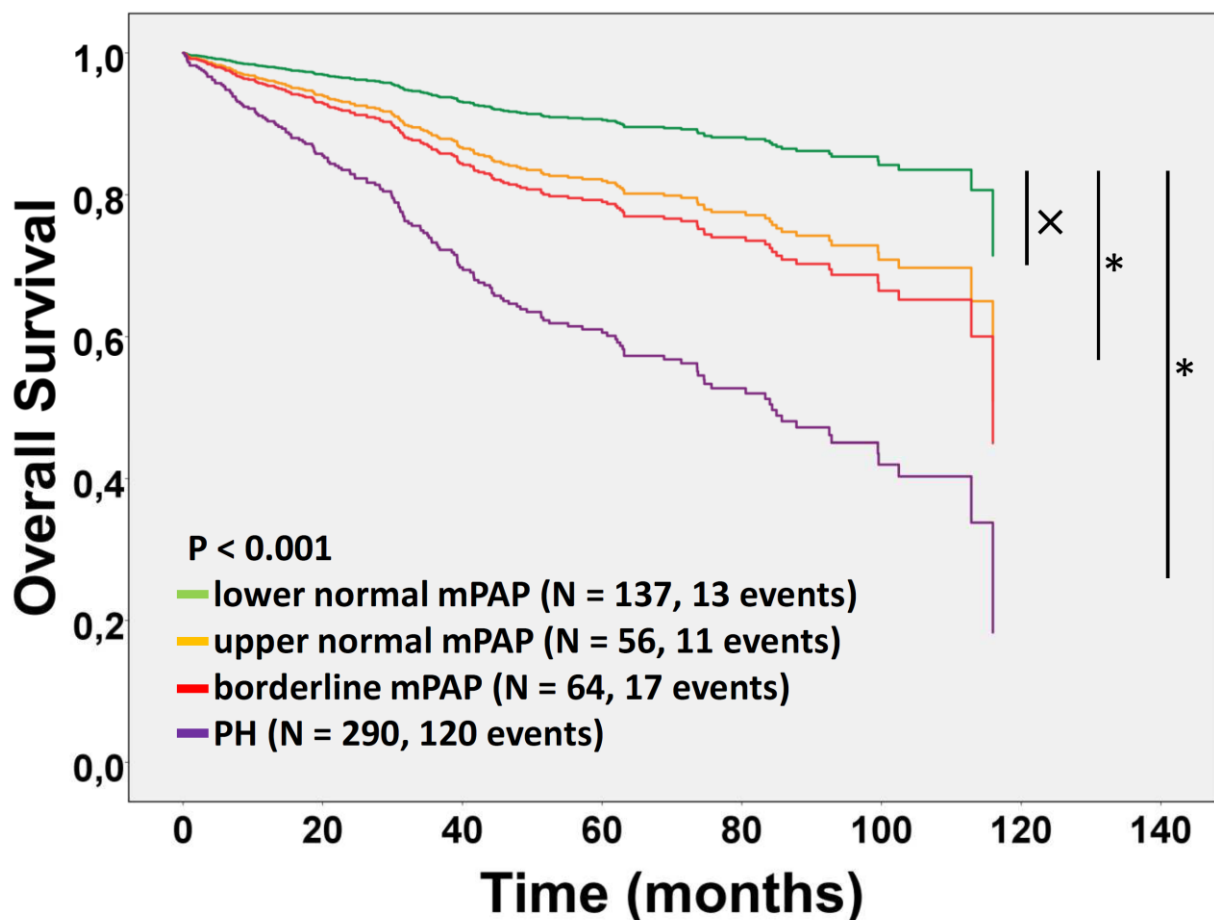


Figure 11: Multivariate COX-Regression analysis by mPAP groups accounting for age and number of comorbidities; * $p < 0.05$; X $p = 0.092$; from (1); Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society.

Discussion

Our study analyzed a retrospectively- as well as a prospectively evaluated collective of patients at risk for PH and/or unexplained dyspnea with a special focus on the clinical impact of mildly elevated pulmonary arterial pressure. All of our patients underwent a set of comprehensive basic clinical investigations including assessment of cardiopulmonary function at rest and during exercise. Furthermore, RHC was performed in every single patient. In a subset of patients not fulfilling resting hemodynamic criteria for pulmonary hypertension exercise hemodynamics were assessed.

As a main result of our study we found that mildly elevated pulmonary pressure starting with a mPAP ≥ 17 mmHg was already associated with increased all-cause mortality. This was mainly driven by age and cardiopulmonary comorbidities. However, mPAP between 21 mmHg and 24 mmHg turned out to be an independent predictor for increased mortality. Besides revealing the prognostic relevance of mildly elevated pulmonary arterial pressure, our study detected some clinical features that are associated with a mildly increased PAP. By assessing clinically relevant cardiopulmonary conditions that may be causative for PH, we investigated their frequency within different mPAP groups. Interestingly there was a significant increase of the number of such conditions within the upper normal- (mPAP: 17 - 20 mmHg) and the borderline- (mPAP: 21 - 24 mmHg) mPAP groups as compared to the lower normal mPAP group. Accordingly, patients within these groups are more frequently suffering from cardiac or pulmonary diseases. The increase of relevant cardiac conditions was furthermore underlined by a slight but significant elevation of PAWP. Another finding of our study was a marked decrease of cardiopulmonary exercise capacity in patients with mildly increased mPAP. Both six-minute walking distance and peakVO₂ showed a stepwise decline reaching its nadir in patients with manifest PH. Although the responsible mechanisms were not fully analyzed within this project, our findings may underline a potential impact of mildly elevated PAP on exercise capacity within this group of patients. Most importantly, by evaluating pulmonary exercise hemodynamics, we could show that concordant with this finding there also were significantly more patients fulfilling criteria for exercise pulmonary hypertension

(mPAP > 30 mmHg + TPR > 3 WU) within the upper-normal- and the borderline mPAP groups.

Our results are in line with findings made previously or shortly after the publication of our study. They underline the clinical importance of mildly altered pulmonary hemodynamics. Moreover, our study together with observations from other groups led to a debate at the world symposium on PH on how to appropriately define pulmonary hypertension and to a change of the definition of pulmonary hypertension.

Within this chapter the following issues will be discussed:

- How to appropriately define pathological pulmonary hemodynamics by the upper limit of normal for mPAP
- The prognostic relevance of borderline mPAP across different disease entities
- The characteristics of patients presenting with mildly elevated PAP
- The relevance of exercise PH in this subset of patients
- Mildly elevated PAP as risk factor for PH
- Therapeutic consequences of mildly elevated PAP
- Limitations of the present study

The upper limit of mPAP

PH was initially defined by mPAP > 25 mmHg. This cut-off was chosen by consensus at the first WHO meeting for PH in 1973 in Geneva in order to avoid overdiagnosis of PH. At this time the physiological mPAP was considered to be much lower (3). However, it was stated that pulmonary hypertension may be definitely present once mPAP is above 25 mmHg. Within the following decades, this cut-off was slightly changed to mPAP ≥ 25 mmHg and it remained the same until recently (2). Although not based on evidence, this cut-off was later on chosen for clinical data bases and pharmaceutical studies. Accordingly, most data available on epidemiology, prognosis

and treatment of pulmonary vascular disease were based on this cut-off and may therefore not reflect the full spectrum of PH.

Hence, new approaches are needed to define this pathological condition. One option is to define pathological pulmonary pressures and PH by a comprehensive overview of hemodynamic data from healthy subjects. In the 1973 statement from the WHO working group for PH, it was already stated that under physiological conditions, in healthy subjects, mPAP does not exceed 15 mmHg at rest (3). Moreover, mPAP was considered to be age independent and “almost never exceeds 20 mmHg”. In 2009, a systematic literature review and metaanalysis aimed to question this paradigm (14). Overall 1187 subjects free of symptoms or major medical conditions were included by the authors. MPAP was found to be independent from age and sex. The weighted mean and standard deviation were 14.0 ± 3.3 mmHg. Therefore, the authors of the study concluded that, from a statistical point of view, the upper limit of normal of mPAP could be set at 20.6 mmHg corresponding to the weighted mean + 2-times the weighted standard deviation. Based on the Gaussian distribution of mPAP, only 2.5% of normal subjects may show mPAP > 20.6 mmHg. These results were in line with the reported physiological thresholds from the first WHO statement. The 20 mmHg cut-off for defining the upper limit of physiological mPAP was thereafter used in several studies investigating the relevance of mildly elevated mPAP (11,140,141). Accordingly, such thresholds were also used in our analysis as literature-based cut-offs in order to make our data comparable to these former collectives (1). Interestingly, our unbiased tree-based approach for prognostic mPAP cut-offs specific for our collective revealed mPAP cut-offs at 16.5 mmHg and 26.5 mmHg. The 16.5 mmHg cut-off is almost identical with the reported weighted mean of mPAP + the 1st weighted standard deviation, whereas the second cut-off fits to the previously used cut-off for PH (25 mmHg) (2,14).

Borderline mPAP as prognostic marker

Another approach may use cut-offs associated with poor clinical outcome such as mortality. Based on the results from our study, mPAP between 21 mmHg and 24 mmHg predicts poor prognosis, independent from age and relevant cardiopulmonary comorbidities (1). Most recently, it has been proposed at the world conference for PH

in Nice, 2018, to change the mPAP cut-off for PH from ≥ 25 mmHg to > 20 mmHg (142,143). The prognostic relevance of mildly elevated PAP was supported by a broad spectrum of studies dealing with borderline mPAP in different conditions (Table 14).

First evidence came from patients suffering from chronic lung disease such as pulmonary fibrosis or COPD. In 1981, Weitzenblum and colleagues published data from a collective of 175 patients with COPD who underwent RHC between 1968 and 1972 (9). 4- and 7-year survival rates were reported. Interestingly, mPAP was not inferior to FEV1 and PaCO₂ in predicting survival of COPD patients. A mPAP of 20 mmHg was identified as optimal cut-off in the prediction of prognosis (4-year survival: 72% vs. 49%, 7-year survival: 56% vs. 29%; $p < 0.01$). 20 years later, a similar study, now following up 61 IPF patients between 1991 and 2004 was published (10). In their analysis, exceeding an mPAP of 17 mmHg turned out to be critical for prognosis. 5-year survival rates were 62% in the mPAP < 17 mmHg group vs. 17% in the mPAP ≥ 17 mmHg group. Besides mortality, mPAP also seems to be associated with the rate of exacerbation in chronic lung disease. In a study by Kessler et al., 64 patients underwent follow-up after an initial evaluation with RHC (8). In their multivariate approach, mPAP, besides PaCO₂, turned out as the only predictor of exacerbation. The cut-off discriminating best was found at 18 mmHg. The relative risk of exacerbation within the higher mPAP group was 2.0 (95% CI: 1.3 – 3.1, $p = 0.0013$).

Similar to chronic lung disease, mildly elevated mPAP seems to be of prognostic relevance in left heart disease. In 1992, Abramson et al. published an echocardiography study with 108 consecutive patients suffering from dilative cardiomyopathy and assessed survival- and hospitalization rates (144). A tricuspid regurgitation velocity (TRV) > 2.5 m/s corresponding to mPAP > 20.3 mmHg turned out to be prognostic for both endpoints. 28 months survival-rates and hospitalization rates were 57% vs. 17% and 75% vs. 26% in the low- vs. high TRV group, respectively. Moreover, in the multivariate model, TRV was the only independent predictor for mortality and hospitalization. In the publication by Kjaergaard et al., patients with an SPAP between 20 and 29 mmHg (corresponding mPAP: 20.9 – 25.2

mmHg) had significantly worse prognosis (145). Again, PAP was an independent predictor of mortality in the multivariate analysis. The same pattern was present in two more studies focusing on patients with left heart disease (146,147). Furthermore, in patients treated with cardiac resynchronization therapy, SPAP > 30 mmHg (mPAP 20.3 mmHg) was associated with higher hospitalization-, transplantation- and poorer survival rates (148).

As shown by these previous studies, there is an association between pulmonary hemodynamics, cardiopulmonary diseases and prognosis. This pattern was also present in our study. We detected a significant increase in the number of both pulmonary and cardiac diseases within the upper-normal- and the borderline mPAP groups compared to the lower-normal mPAP group (Table 14). Furthermore, from the lower-normal to the borderline mPAP group, a significant elevation in PAWP was present. Accordingly, we speculated that this increase in relevant left heart or pulmonary comorbidities together with age might be the driver of mortality in our collective. However, after correction for both types of comorbidities and age, borderline mPAP remained a significant predictor of mortality.

Besides chronic cardiopulmonary disease, borderline mPAP seems to have impact on prognosis in other conditions (Table 14). In patients with sickle cell disease the development of PAH (mPAP \geq 25 mmHg) is a major predictor of survival (149). Several studies in patients with sickle cell disease evaluated the prognostic relevance of TRV and sPAP assessed by echocardiography. They revealed that starting with mPAP \geq 20.3 mmHg (TRV \geq 2.5 m/s) patients had higher mortality rates (150–152). Systemic sclerosis has been strongly associated with the development of pulmonary arterial hypertension. Accordingly, borderline mPAP has been suspected to be a risk factor in scleroderma patients. A recent retrospective study on the prognostic impact of borderline PAP in a collective of patients undergoing RHC at a PH center revealed that patients diagnosed with systemic sclerosis and mildly elevated mPAP (21 – 24 mmHg) are at particular risk of increased mortality (140). Data from other conditions, associated with PAH, are lacking.

Analysis from larger registries including our present study aimed to answer the question whether or not mildly increased PAP is a general predictor of mortality in

mixed collectives also including patients considered to be at risk for PAH (Table 14). Analysis of general populations, using echocardiography, confirmed that mildly elevated PAP is associated with increased risk for death. In 2009, Lam et al. published data from a collective of randomly evaluated subjects from the population of Olmsted County, Minnesota (153). 2042 subjects underwent echocardiography. SPAP turned out to be a strong predictor for mortality (HR 2.73 per 10 mmHg; $p < 0.001$). Above SPAP 30 – 32 mmHg (mPAP 20 – 21.5 mmHg) patients had poorer outcomes. As echocardiographic estimations of PAP may significantly differ from invasively measured PAP, such studies may provide the basis for new concepts but are limited by methodology (127). In the largest so far published analysis on this topic, 21,727 patients from the US Veterans Affairs healthcare system underwent RHC between 2007 – 2012 (13). The prognostic relevance of mPAP was evaluated. The hazard ratios for mortality of each mPAP level were assessed and a steadily increase of mortality above mPAP 19 mmHg was identified. Interestingly, the steepest increase of mortality was found within the mPAP range of 19 mmHg to 24 mmHg, corresponding to borderline PAP. mPAP between 19 and 24 mmHg was not only associated with lower survival rates but also with higher rates of hospitalization. One of the limitations of this study lies within the characteristics of the selected group of patients. The majority of patients were male (96.6%) and the main indication for RHC was work up for valvular heart disease and heart failure. Therefore, this study may not reflect characteristics and features of patients as they are seen in a typical PH clinic dealing with patients at risk for PAH. However, a retrospective single center study based on a PH registry revealed that this may also hold true for patients at risk for PAH (140). These previous findings were confirmed by our present study also including a heterogeneous prospectively evaluated collective as it is usually seen at PH clinics. In a recent metaanalysis summarizing the results of 15 studies dealing with the impact of borderline mPAP on the prognosis of over 16,000 patients, the risk ratio of mortality in the overall collective was 1.52 (95% CI, 1.32 – 1.74; $p < 0.001$) (154).

Reference	Underlying condition	Number of patients	PAP cut off / PAP group	Diagnostic tool	Outcome
Lung disease					
Weitzenblum et al. 1981 (9)	COPD	175	mPAP 20 mmHg	RHC	Mortality ↑
Hamada et al. 2007 (10)	IPF	68	mPAP 17 mmHg	RHC	Mortality ↑
Kessler et al. 1999 (8)	COPD	64	mPAP 18 mmHg	RHC	Exacerbation rate ↑
Left heart disease					
Abramson et al. 1997 (144)	Idiopathic and ischemic CMP	87	TRV 2.6 – 3.0 m/s (mPAP: 21.5 – 27.0 mmHg)	Echo	Mortality ↑, Hospitalization-rate ↑
Kjaergaard et al. 2007 (145)	Heart failure	194	SPAP 31 – 38 mmHg (mPAP 20.9 – 25.2 mmHg)	Echo	Mortality ↑
Damy et al. 2010 (146)	Heart failure	311	TPG 26 – 35 mmHg (mPAP 20.9 – 26.4 mmHg)	Echo	Mortality ↑

Choudhary et al. 2014 (147)	Jackson Heart study	2.567	SPAP 28 – 32 mmHg (mPAP 19.1 – 21.5 mmHg)	Echo	Hospital admissions ↑
Shalaby et al. 2008 (148)	CRT patients	176	SPAP 30 – 44 mmHg (mPAP 20.3 – 28.8 mmHg)	Echo	Mortality ↑, Transplantation-rate ↑, HF-admission ↑
Other Conditions					
Damy et al. 2016 (152)	Sickle cell disease	1.780	TRV ≥ 2.5 m/s (mPAP 20.3 mmHg)	Echo	Mortality ↑
Mixed collectives					
Heresi et al. 2013 (140)	PH clinic	1.491	mPAP 21 – 24 mmHg	RHC	Mortality ↑
Lam et al. 2009 (153)	Population Olmsted County Minnesota	2.042	SPAP 30 – 32 mmHg (mPAP 20 – 21.5 mmHg)	Echo	Mortality ↑
Maron et al. 2018 (13)	US-Veterans	9.237	mPAP 19 -24 mmHg	RHC	Mortality ↑, Hospitalization-rate ↑
Douschan et al. 2018 (1)	PH clinic	547	mPAP 21 – 24 mmHg	RHC	Mortality ↑

Table 14: Summary of clinical studies dealing with outcome in patients with mildly elevated PAP; Echo: echocardiography, RHC: right heart catheterization, TRV tricuspid regurgitation

velocity, TPG: tricuspid pressure gradient, SPAP: systolic pulmonary arterial pressure, mPAP: mean pulmonary arterial pressure;

Characteristics and phenotypes of mildly elevated mPAP

Our study indicates that besides their impact on overall survival, upper-normal mPAP as well as borderline mPAP patients differ significantly from patients with normal pulmonary hemodynamics (Tables 10 - 13). Patients with such mildly elevated mPAP values were significantly older and had a higher number of cardiopulmonary comorbidities. A similar pattern of characteristics has been recently described in other collectives (155). Rates of cardiopulmonary comorbidities were similar to previously published data from the REVEAL registry (156). NTproBNP, an established biomarker for cardiac strain, showed a steady increase from the lower-normal mPAP group to manifest PH with intermediate high NTproBNP in patients with upper-normal- and borderline mPAP. Besides left cardiac conditions causing an elevation of NTproBNP, the right ventricle may be the origin of elevated NTproBNP. Tissue Doppler studies on patients with borderline mPAP recently showed beginning RV dyssynchrony in patients with mildly elevated mPAP (157).

Moreover, exercise performance assessed by 6-minute walking test and cardiopulmonary exercise testing were significantly decreased in patients with mildly elevated mPAP. Exercise limitation and exertional dyspnea may be the earliest symptoms and signs of pulmonary vascular disease. Lau and colleagues reported that 90% of patients with borderline PAP have exertional dyspnea NYHA II-III (158). In a former study, our group showed that in patients at risk for precapillary PH, suffering from systemic sclerosis, mPAP > 17 mmHg was associated with poor exercise performance as demonstrated by a low peakVO₂ and decreased 6MWD (12).

In our population, resting hemodynamics showed significant differences between the mPAP groups not only in terms of mPAP. In the majority of cases, within the upper-normal and borderline mPAP groups, slight elevation of mPAP may be caused by the underlying cardiac- and pulmonary condition and may therefore be considered secondary. This assumption is supported by a slight increase of PAWP between these groups perhaps due to impairment of the left ventricular diastolic function.

Previous studies showed similar results and reported associations between age, E/e' and PAP on echocardiography (153). As for manifest PH (see introduction) it can be speculated that the vast majority of patients presenting with a borderline mPAP may be composed of patients with chronic left heart- or chronic pulmonary disease (Figure 12). Left heart disease may still be hemodynamically occult at this stage as suggested by normal or almost normal PAWP at RHC. It may be, however, unmasked using exercise tests or volume challenge (159,160). Nevertheless, there was a considerable number of patients with an elevated PVR > 3 WU within the upper-normal- and borderline mPAP groups in our study (Figure 5). This indicates that early isolated pulmonary vascular disease may also be present as a small subset within this patient group (Figure 12). This may be of special interest in the setting of collagen vascular disease such as systemic sclerosis or patients with chronic thromboembolic disease where mildly elevated PAP could be considered a precursor of manifest PH (11,141,161). The probable distribution of different phenotypes of PH across different mPAP stages is shown in Figure 12.

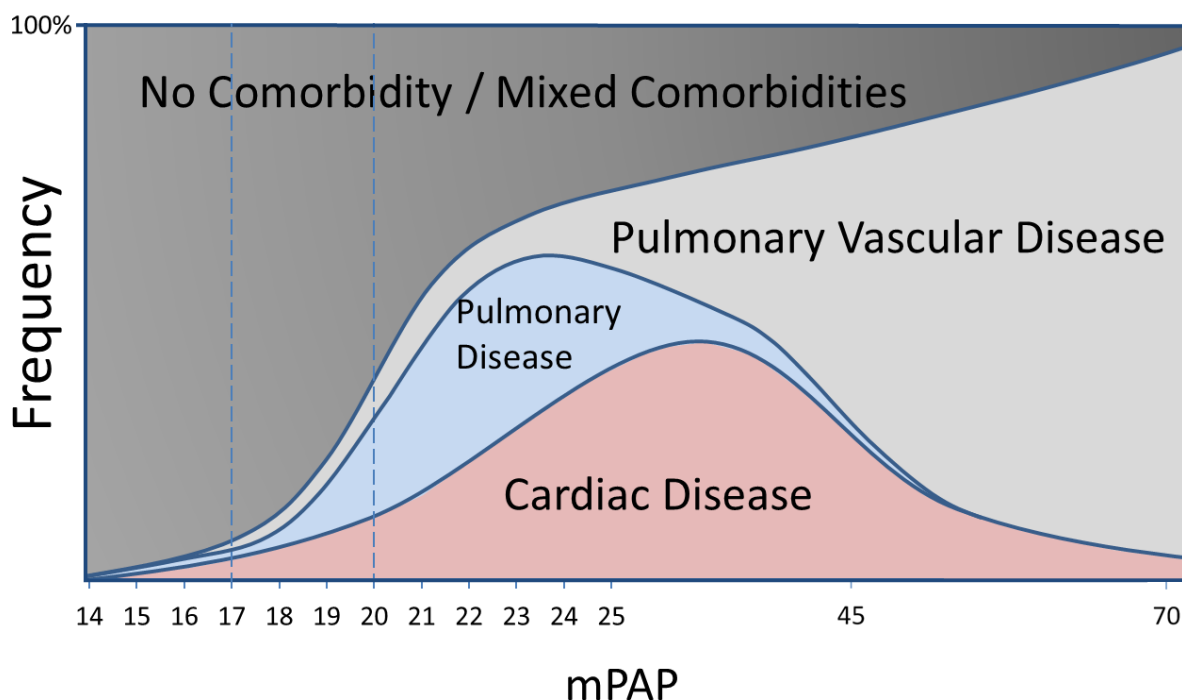


Figure 12: Probable frequency of different phenotypes across mPAP levels; Within the upper-normal mPAP region (17 – 20 mmHg) the frequency of patients suffering from cardiopulmonary comorbidities is increasing; Within the borderline mPAP region (21 – 24

mmHg) left heart disease and chronic pulmonary disease may dominate; However, there may be an increasing number of patients with primary pulmonary vascular disease (PVD) present;

Exercise hemodynamics and mildly elevated PAP

In our heterogenous collective the reason for poor exercise performance may be multifactorial. However, most recently, an abnormal pulmonary hemodynamic response to exercise has been linked to physical limitations and symptoms in patients with mildly elevated PAP at rest (158). Under physiological conditions, mPAP during exercise rarely exceeds 30 mmHg (14). At the 4th world symposium on PH the term “exercise pulmonary hypertension” (EPH) was abandoned as mPAP during exercise > 30 mmHg seemed too unspecific to characterize this patient group and there was not enough evidence to support this threshold (162). In the following years, a new definition was proposed, also taking into account the cardiac output during exercise (21). Analysis of historical healthy volunteers, controls without heart lung disease, patients with left heart disease and patients with known pulmonary vascular disease revealed that a mPAP > 30 mmHg together with a total pulmonary resistance (TPR) > 3 WU may be the best criteria to define EPH (20). EPH was associated with poor exercise tolerance in several patient collectives. There seems to be a strong association between EPH and resting borderline pulmonary pressure at rest. In a recent study, EPH was present in 86% of patients with borderline PAP (158). A similar distribution was found in our collective, were the rates of EPH based on recent hemodynamic criteria in the lower-normal-, upper-normal- and borderline mPAP groups were 40%, 73% and 89%, respectively. The high number of patients with EPH within the lower-normal mPAP group could be explained by our selection criteria. For ethical reason no healthy controls were included in our study. Patients recruited were suffering from unexplained dyspnea or were considered to be at risk for pulmonary vascular disease. Unfortunately, EPH is not specific for pulmonary vascular disease but may also be seen in other conditions like left heart disease where normal pulmonary hemodynamics at rest can be unmasked during exercise. EPH, in these patients, is primarily driven by a steep increase of PAWP due to pulmonary venous congestion during exercise. EPH was described in up to 88% of patient with HFpEF and normal resting hemodynamics (159). However, there may

also be cases with occult combined pre- and post-capillary phenotypes of left heart disease within the borderline PAP collectives. In patients with chronic lung disease, especially in patients suffering from chronic obstructive disease, EPH is primarily driven by hyperinflation of the lungs during exercise (139,163,164). This means that there is a dynamic increase of intrathoracic pressure when patients do exercise. Another condition where EPH may contribute to exercise impairment is chronic thromboembolic disease (CTED) (165). Patients with CTED suffer from persistent chronic thrombotic changes similar to CTEPH with a mPAP below 25 mmHg at rest. EPH was reported in 75% of patients diagnosed with CTED (166). In general, the functional impact of EPH and borderline PAP at rest seems to be similar (167).

Borderline PAP as precursor of manifest PH

Our study did not provide data on follow-up. It has been speculated that manifest PH may represent an advanced stage and borderline PAP could be interpreted as an early stage of pulmonary vascular disease. Most recently a perinatal origin of PAH has been discussed. Adverse perinatal events may cause damage on early pulmonary vasculatures and make it more susceptible for triggers of adult pulmonary vascular disease. A good example for such a disease is bronchopulmonary dysplasia (BPD). Preterm infants are at increased risk for developing this condition which is characterized by an impaired development of airspace and pulmonary vessels. Placental underperfusion during pregnancy has been linked to BPD and seems to cause damage on the fetal pulmonary vasculature. In case of placental underperfusion, markers such as VEGF, granulocyte-colony stimulating factor (G-CSF) and placental growth factor (PIGF) are decreased in the cord blood. A decrease in these factors is associated with higher rates of BPD and PH (168). Studies on preterm infants found significantly increased rates of PH 7 days and 36 weeks after birth, 42% and 14%, respectively (169). Early PH at day 7 was a risk factor for persistent PH and severe BPD at week 36. Signs of early pulmonary vascular disease, 7 days after birth, are also associated with higher rates of lung related hospitalizations, exacerbations of BPD, asthma, bronchiolitis, pneumonia and reactive airway disease within the first two years of childhood (170). There is not only evidence for increased rates of cardiopulmonary complications during childhood: Abnormal development of fetal and perinatal pulmonary vasculature also seems to

influence the cardiopulmonary circulation during adulthood. The cardiac function in young adults, born preterm, is altered with significantly altered diastolic and systolic functional properties as well as changes in the left ventricular architecture (171). Cardiac reserve as assessed by cardiac output, EF and LV peak longitudinal strain during exercise is impaired (172). These changes seem to be associated with slightly but significantly higher rates of heart failure during adulthood (173). There is also susceptibility for pulmonary vascular and right heart abnormalities in this subset of patients like increased right ventricular mass and lowered RV cardiac output and EF (174). The advent of manifest PH as consequence of impaired airspace- and pulmonary vasculature development has also been described. Analysis of the Swedish Medical Birth Registry revealed a significant association of premature birth and the diagnosis of PH during adulthood (OR = 8.46, 95% CI, 2.97 – 24.10, $p < 0.001$) (175). Furthermore, a recent study demonstrated that up to 27% of preterm subjects may have a mildly elevated mPAP between 19 and 24 mmHg (176).

The concept of borderline PAP being a risk factor or precursor of manifest PH has also been discussed in other phenotypes of pulmonary vascular disease. Systemic sclerosis is a condition, frequently associated with PAH. Follow-up studies revealed high rates of conversion from borderline PAP to manifest PH in this group of patients (11,141). In one study, the reported rates of progression to PAH were 8.3% at 3 years and 14% at 5 years (11). A second study reported conversion rates of patients from an initial mPAP < 25 mmHg to PAH in a median time of 3 years of 7% (141). However, in the same collective, overall 25.3% developed PH. This report underlines that mildly increased PAP is not only a risk factor for developing PAH but also other forms of PH. In a large single PH center follow-up study using RHC data from 4343 subjects this pattern of high conversion rates from mildly elevated PAP to manifest PH was confirmed (155). 61% of the patients with initial borderline PAP developed manifest PH (mPAP \geq 25 mmHg). Precapillary PH was diagnosed in 21% of these patients, whereas 79% developed postcapillary PH. There were also some patients (20%) where hemodynamics improved from mildly elevated mPAP to normal mPAP (\leq 18 mmHg).

In summary, fetal and perinatal development of the pulmonary circulation may be key-factors for pulmonary vascular disease during adulthood. Moreover, borderline PAP per se seems to be a risk factor for several hemodynamic forms of manifest PH in adulthood. A schematic concept for the development of pulmonary vascular disease over time is shown in Figure 13.

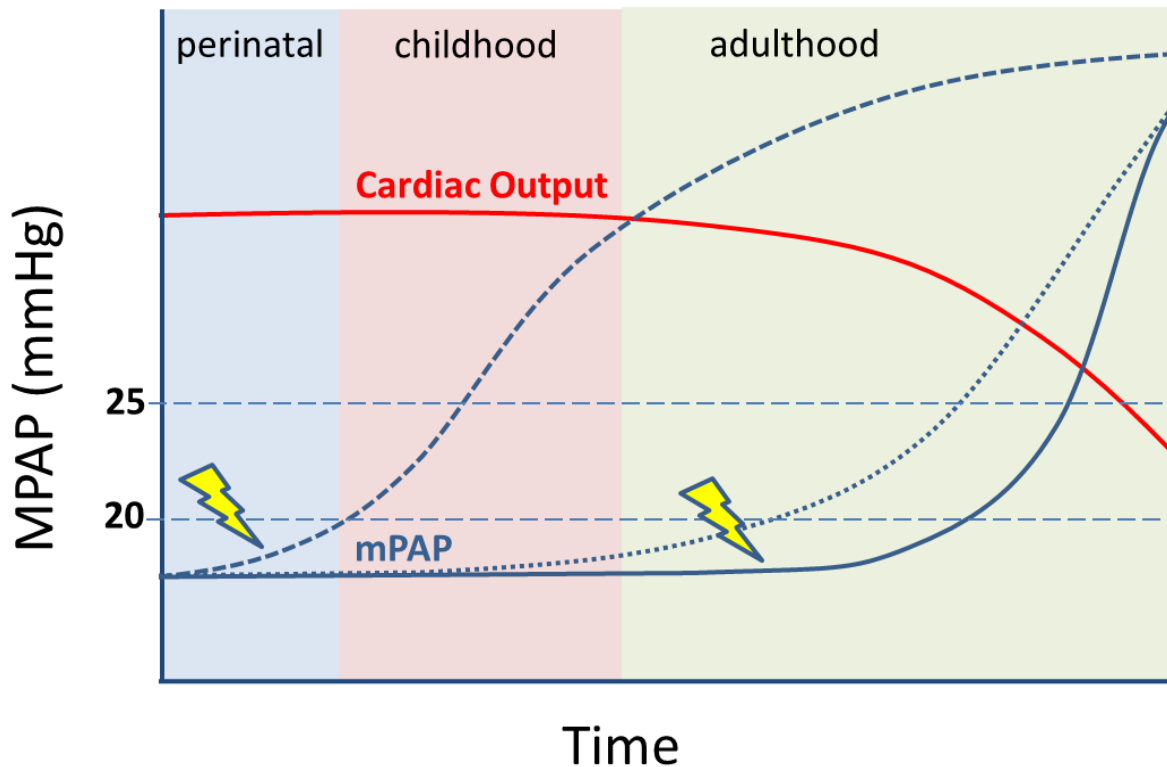


Figure 13: Development of pulmonary vascular disease. Perinatal Triggers (e.g.: BPD) may lead to development of childhood-PAH (dashed lines). Patients with genetic predisposition or risk factors PAH may develop PAH during adulthood (spotted line). Moreover, PAH may develop in patients with a trigger during adulthood (e.g.: recurrent PE, drug-induced damage) (continuous line). Cardiac output decreases during disease progression (red continuous line).

Concepts to handle borderline PAP

Our results together with evidence provided by previous studies lead to the question, how to handle patients diagnosed with borderline PAP. The natural history of mildly elevated PAP with many patients suffering from dyspnea and impaired exercise capacity, the high conversion rates to manifest PH and most importantly the impact on overall survival may be arguments to ask for therapeutic interventions

(1,13,155,158,167). However, borderline PAP per se represents a heterogeneous collective of patients. In the majority of cases, PAP elevation is secondary rather than a sign of a primary pulmonary vascular disease (Figure 12). In these collectives, treatment of the underlying condition with optimization of left heart disease and/or chronic pulmonary disease is the treatment of choice. Vasoactive drugs may worsen left cardiac function or lead to increased V/Q mismatch in patients with chronic lung disease. Accordingly, interventions with pulmonary vasoactive drugs should be avoided in the general collective of patients with mildly elevated mPAP. There may, however, be subsets of patients such as systemic sclerosis or chronic thromboembolic pulmonary disease (CTED), where borderline PAP represents a precursor of severe pulmonary vascular disease (11,165). In CTED, surgical interventions lead to an improvement of hemodynamics and exercise capacity (161), however, evidence for pharmaceutical treatment in these patients is weak. One small prospective study evaluated the safety of PAH medication (bosentan) in borderline scleroderma patients (177). Pulmonary hemodynamics improved and no adverse events were observed, but there was no functional improvement. There is no recommendation for PAH drugs in these subsets of patients as any positive results from larger prospective randomized trials are still missing. So far, close follow-up of patients with borderline PAP at risk for PAH is the only recommendation. In order to perform pharmaceutical trials, patients that may profit from PAH drugs need to be adequately defined.

Based on the available data it was recommended to change the definition of precapillary PH (mPAP > 20 mmHg, PAWP ≤ 15 mmHg, PVR ≥ 3 WU) at the 6th world symposium of PH, Nice, 2018 (143). Now trials are needed to clarify whether or not patients with mild precapillary PH, in the absence of relevant left heart and pulmonary disease, profit from PAH drugs (178).

Limitations

Our study has several limitations. First, no control subjects or healthy controls were included. For ethical reasons, RHC should not be performed in healthy subjects. Moreover, our collective represents a selective group of patients. Accordingly, there may be a referral bias into our study. Our PH clinic focuses on patients at risk for PH

and/or otherwise unexplained symptoms that may be associated with pulmonary vascular disease and may be candidates for PAH drugs. Patients with severe left heart disease were excluded from RHC as PAH drugs are not recommended for these patients. Therefore, patients with severe left heart disease may be underrepresented. To rule out that cardiopulmonary comorbidities may interfere with our survival analysis, we needed to define relevant cardiac and pulmonary conditions, based on recent guidelines and recommendations (106). However, this may not have addressed the whole spectrum of conditions. We did not consider different phenotypes of obstructive lung disease, the frequency of pulmonary exacerbations or metabolic disease. Still to our knowledge this is the first study performed in patients at risk for PH together with manifest PH without preset thresholds the retrospectively and prospectively evaluated the impact of pulmonary arterial pressure on the most important outcome, all-cause mortality.

Conclusion and impact of the study

In conclusion, in this first study with a combined retrospective and prospective analysis we showed that mild changes in resting hemodynamics are significantly associated with a poor outcome. In patients with upper-normal mPAP this was mainly driven by older age and more cardiopulmonary comorbidities. Borderline mPAP, within the range of 21 and 24 mmHg, however, turned out to be an independent prognosticator of a poor outcome. Furthermore, we characterized patients with mildly elevated PAP and confirmed results from previous studies. At the 6th world symposium on pulmonary hypertension in Nice, 2018, our study, together with other previously published investigations, led to a change of the hemodynamic definition of pulmonary hypertension with a new mPAP cut-off at 20 mmHg.

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