“Impact of prolonged waiting times for surgery during the COVID-19 pandemic on preoperative pulmonary hemodynamics and postoperative outcome of patients with chronic thromboembolic pulmonary hypertension undergoing pulmonary endarterectomy”

Inauguraldissertation
zur Erlangung des Grades eines Doktors der Medizin
des Fachbereichs Medizin
der Justus-Liebig-Universität Gießen

Vorgelegt von Tsimpoura, Paraskevi
Aus Kalampaka, Griechenland

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DEDICATION

To my loving father, Tasos,

who always supported,

encouraged

and believed in me

Table of contents

1 Introduction ... **1**

1.1 Chronic Thromboembolic *Pulmonary Hypertension* ... *1*
1.1.1 Definition, epidemiology and classification ... 1
1.1.2 Pathophysiology ... 4

1.2 The path to diagnosis ... *6*
1.2.1 Therapeutic options and prognosis ... 12
1.2.1.1 Surgical treatment ... 12
1.2.1.2 Interventional treatment ... 13
1.2.1.3 Pharmacological treatment ... 14
1.2.1.4 Multimodal therapy ... 14

1.3 Pulmonary Endarterectomy (PEA) ... *15*
1.3.1 How it all began ... 15
1.3.2 Perioperative management of pulmonary endarterectomy ... 17

1.4 Corona Virus Disease-19 pandemic ... *20*
1.4.1 COVID-19 worldwide ... 20
1.4.2 COVID-19 in Germany ... 21

1.5 Aim of the study ... *22*

2 Material and methods ... **23**

2.1 Study *design* ... *23*
2.1.1 Study population, inclusion and exclusion criteria ... 23
2.1.2 Data collection ... 25
2.1.3 Definition of primary and secondary endpoints ... 28
2.1.4 Software ... 30
2.1.5 Statistical plan ... 30

3 Results ... **32**

3.1 Demographic data ... *32*

3.2 Patient characteristics ... *32*
3.2.1 Sex, Age ... 32
3.2.2 Comorbidities ... 32

3.3 CTEPH specific characteristics ... *32*
3.3.1 WHO classification ... 32
3.3.2 Long-time oxygen therapy ... 33

3.4 Surgical *characteristics* ... *33*

3.5 Waiting time ... *35*
3.5.1 Waiting time from onset of symptoms to surgery ... 35
3.5.2 Waiting time from CTEPH diagnosis to surgery ... 35
3.5.3 Time interval between the measurements ... 36

3.6 Primary endpoint ... *37*

3.7 Secondary endpoints ... *40*
3.7.1 ICU stay ... 40
3.7.2 Mortality ... 40
3.7.3 Perioperative complications ... 41
3.7.3.1 MACE ... 41
3.7.3.2 Reperfusions oedema ... 41
3.7.3.3 ECMO ... 42

4 Discussion ... **43**

4.1 The COVID-19 pandemic ... 43

4.2 Primary endpoints ... 46
4.2.1 Time intervals ... 46
4.2.2 Pulmonary haemodynamic ... 47

4.3 Primary endpoints ... *50*
4.3.1 Mortality ... 50
4.3.2 ICU stay ... 50
4.3.3 MACE ... 51
4.3.4 Reperfusion oedema ... 51
4.3.5 ECMO support ... 52

4.4 Study limitations ... *53*
4.4.1 Study design ... 53
4.4.2 Haemodynamic measurements ... 54

4.5 Perspective ... *55*

5 Abstract ... **56**

6 Zusammenfassung ... **57**

7 List of abbreviations ... **58**

8 Table directory ... **61**

9 List of illustrations ... **62**

10 Danksagung ... **63**

11 Bibliography ... **64**

1 Introduction

1.1 Chronic Thromboembolic Pulmonary Hypertension

1.1.1 Definition, epidemiology and classification

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is a symptomatic form of precapillary pulmonary hypertension (PH) which appears with persistent pulmonary perfusion defects after acute pulmonary embolism (PE) despite adequate anticoagulation for at least 3 months. It is characterized by a mean pulmonary artery pressure greater than 20 mmHg and pulmonary vascular resistance greater or equal to 2 Wood Units (WU) (= 160 dyn·s/cm5). (68) Further, several studies suggest that within two years after occurrence of PE a percentage of 0.9 to 8.8% patients will have developed CTEPH. (23)

The disease is characterised by stenosis and / or occlusion of the pulmonary artery vessels due to unresolved thrombi after acute or recurrent PE and/or deep venous thrombosis. As a result, fibrotic remodelling of the pulmonary vessels and an increase of pulmonary vascular resistance and pulmonary artery pressures develop in these patients. The epidemiology of CTEPH worldwide is unknown as it seems to be largely underdiagnosed and therefore underreported and undertreated. The incidence of CTEPH from data from the USA, Europe and Japan as reported in the CTEPH registry is estimated to be 10 cases per 1.000.000 adult population. (13) Specifically in Germany the incidence of CTEPH was in 2016 5.7 cases per 1.000.000 adult population. (47) There seems to be no gender differences in the USA and Europe; however, in Japan almost 75% of the patients are female. (24)

Conditions that have been identified as risk factors for CTEPH are as shown in detail in table 1: ventriculo-atrial shunts, splenectomy, intracardiac pacemakers, history of prolonged hospital stay, polytrauma, malignancies, thyroid replacement therapy and several coagulation abnormalities. (45)

Acute pulmonary embolism	Haemostatic factors	Co-existing medical conditions
- Pulmonary artery pressures at the time of diagnosis higher than an unadjusted right ventricle can develop - Recurrent PE events - Idiopathic PE	- Elevated factor VIII - Elevated von Willebrand factor - Variation in fibrinogen expression - Non-O blood group - Elevated level of lipoprotein (a)	- Previous or recurrent venous thromboembolism - History of splenectomy - History of malignancy - Hypothyroidism under thyroid replacement therapy - Presence of ventriculoatrial (VA) shunts - Staphylococcal infection - Chronic inflammatory bowel disease - Osteomyelitis - Antiphospholipid syndrome - Elevated inflammatory markers: C-reactive protein (CRP), interleukin (IL)-1b, IL-2, IL-4, IL-8, IL-10

Table 1: Risk factors associated with CTEPH. CRP: C-reactive protein, IL: interleukin, PE: pulmonary embolism, VA: ventriculo-atrial). (45)

CTEPH is classified as subgroup 4 (PH due to chronic pulmonary artery obstruction) in the updated classification of pulmonary hypertension in 2019 (68) (see table 2). It is the only possibly curable form of PH.

Group 1: Pulmonary Arterial Hypertension (PAH)	1.1 Idiopathic 1.2 Heritable PAH 1.3 Drug- and toxin-induced PAH 1.4 PAH associated with: Connective tissue disease HIV Infection Portal hypertension Congenital heart disease 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 new-born syndrome
Group 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
Group 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
Group 4: PH due to pulmonary artery obstructions	4.1 Chronic thromboembolic pulmonary hypertension (CTEPH) 4.2 Other pulmonary obstructions
Group 5: PH with unclear and/or multifactorial mechanisms	5.1 Haematological disorders 5.2 Systemic and metabolic disorders 5.3 Others

Table 2: Updated classification of PH (modified by Simmonneau et al. (68)). HIV: human immunodeficiency virus, LVEF: left ventricular ejection fraction, PAH: pulmonary arterial hypertension, PH: pulmonary hypertension, PCH: pulmonary capillary hemangiomatosis, PVOD: pulmonary veno-occlusive disease.

All patients suffering from PH (including CTEPH) are further assigned to a World Health Organisation (WHO) functional class in order to describe how the disease affects their daily life. It is also used to monitor effectiveness of PH therapy and is one of various determinants of the prognosis for patients suffering from PH. The WHO functional class system includes four functional classes with class 1 being the mildest and class 4 the most severe. A further use of the WHO FC system is to assist in risk assessment. A detailed description of the WHO functional class system, made by the European pulmonary hypertension association, is listed in table 3. (17)

Class I	Symptom-free when physically active or resting
Class II	No symptoms at rest, but normal activities such as climbing the stairs, grocery shopping or making the bed cause some discomfort and shortness of breath
Class III	Resting may be symptom-free, but normal chores around the house are greatly limited due to shortness of breath or feeling tired
Class IV	Symptoms at rest and severe symptoms with an activity

Table 3: WHO functional classification modified by (17).

1.1.2 Pathophysiology

The exact pathophysiological mechanisms that lead to CTEPH are yet to be completely explained, although a lot of progress is made through ongoing research in this field. According to the current state of research CTEPH is a disease that slowly progresses over time and in about 75% of cases results as a late complication of an acute PE. (69)

Acute pulmonary embolism commonly follows a deep venous thrombotic event and frequently remains unnoticed. Thrombus material from the initial embolic event obstructs the pulmonary circulation resulting in PE. In most of the cases when proper anticoagulation is applied and the endogenous fibrinolytic mechanisms are activated the thrombi resolve within a few weeks and the clinical condition improves. Contrariwise in CTEPH the thrombi do not resolve at all or only resolve partially leading to a complete or subtotal occlusion of the affected arteries. (69)

The mechanisms that lead to this dysfunction are not yet known; however, several risk factors have been identified (shown in Table 1). Regarding the molecular basis of the dysfunctional pulmonary endothelium, the nitric oxide (NO)-soluble Guanylate Cyclase-cyclic Guanosine Monophosphate (sGC-cGMP), the endothelin (ET)–1 and prostacyclin (PGI_2) pathway seem to play a major role in the pulmonary vessels.

The unresolved thrombotic material remains firmly attached to the intima of the elastic pulmonary arteries, with a diameter greater than 500 μm, and subsequently undergoes a complex remodelling. This in turn triggers a secondary microvasculopathy and seems to be the cardinal mechanism causing the increase of pulmonary vascular resistance (PVR) and progression of the disease. Galiè et al have identified three types of vascular lesions that contribute to CTEPH:

i. Mainly obstructions of subsegmental elastic pulmonary arteries
ii. Classical pulmonary arteriopathy of small muscular arteries and arterioles distal to non-occluded vessels
iii. Micro vessel disease distal to totally or partially obstructed vessels

Later, Simonneau et al. have further distinguished the vessel disease in intra-vascular arteriopathy of main, lobar, segmental and subsegmental pulmonary arteries and secondary micro vessel disease, which is located distal to the occlusion and in the small arterioles, capillaries and venules of the non-occluded vessels. (18)

The occlusion of the pulmonary arteries by unresolved, fibrotic, thrombotic material can extend from main pulmonary arteries down to distal arteries at the intra-acinar level. On the distal level a recanalization of the occluded arteries with building of secondary lumina has been observed. Interestingly, this type of clot is completely different from the fresh organised clots; yellow in colour containing elastin, collagen, inflammatory cells and sometimes calcifications. In contrast to a fresh thrombus, these clots are firmly attached to the internal artery wall, making it impossible to be removed in any other way than pulmonary endarterectomy.

Next to the damage due to thrombotic occlusion of pulmonary arteries, the vasculopathy in the non-occluded vessels has an even more detrimental effect on the increase of PVR and the progress of the disease. This remodelling constitutes of fibrotic remodelling and also fibromuscular proliferation of the intima. The lesions have a partially plexiform pattern which might indicate the presence of bronchopulmonary shunts. (67) This remodelling in non-occluded arteries can be accredited to the shear stress produced by increased local flow and pressure due to redistribution of blood flow from the obstructed to the non-obstructed vessels; a much similar condition to left-to-right cardiac shunt.

Another important component in the development of CTEPH is the bronchial circulation which is a lot more than a bystander in the course of the disease. The decrease in the pulmonary artery pressure distal to the occlusion with the parallel

increase in the pressure gradient between bronchial and pulmonary arteries seem to reopen pre-existing bronchopulmonary anastomoses.

This reopening is practically a thoroughfare for the transmission of systematic pressures to low pulmonary venous pressures, that leads to arterialization of the pulmonary venules.

The microvasculopathy in territories distal to occluded arteries has been described as a result of hemangiomatosis-like capillary remodelling and pulmonary veno-occlusive disease like pulmonary venules' remodelling. These anastomoses between hypertrophic bronchial arteries and pulmonary circulation help sustain the viability of the lung tissue distal to the occlusion by keeping the capillary bed open.

Ultimately, the dysfunction of pulmonary endothelium, occlusion of pulmonary arteries and vasculopathy of non-occluded vessels all lead to a progressive increase in PVR which in turn results in right ventricular remodelling and failure; and finally, in symptomatic CTEPH.

1.2 The path to diagnosis

CTEPH is an often underdiagnosed or late-diagnosed disease. The reason for delayed diagnosis is not only the slow progression and rarity of the disease, but also the rather general or unspecific cardinal symptom: Dyspnoea on exertion. The symptom worsens over time and is frequently misinterpreted or contributed to lack of exercise, low fitness level and other more common diseases such as obesity, bronchial asthma or chronic obstructive pulmonary disease (COPD). (46) Other symptoms of CTEPH are fatigue, depression, and signs of right heart failure, such as peripheral oedemas or syncope (see Table 4).

Clinical Symptoms of CTEPH		
Early stage:	**Later stage:**	**Severe cases:**
- Dyspnoea on exertion - Chest pain/discomfort after exertion - Fatigue - Palpitations - Dry cough - Dizziness	- (Pre-)Syncope after exertion - Peripheral oedemas - Jugular vein distention - Ascites - Acrocyanosis	- Syncope - Dyspnoea with moderate activity - Haemoptysis - Right ventricular failure

Table 4: Clinical symptoms of CTEPH. *(35)*

Because of the long time from onset of symptoms until medical examination and correct diagnosis, in most cases the disease has drastically progressed. Over 70% of patients are already classified in WHO Function class III or IV at the time of diagnosis. Due to rising knowledge and awareness in recent years, physicians have become more alert and the disease is diagnosed in earlier stages, accompanied with better prognosis for patients. A mean delay of 18 ± 26 months between onset of symptoms and diagnosis of CTEPH has been reported, with a slightly bigger delay in patients without a history of acute PE (23.5 ± 36.9 months vs. 16.9 ± 23.8 months in patients with history of acute PE). (33)

A diagnostic algorithm for CTEPH has been designed at the 2016 Consensus Conference and updated in the 2022 ESC/ERS Guidelines for the diagnosis and treatment of PH (see Figure 1). (36) The patient's history along with several symptoms and findings in screening clinical and medical examination such as electrocardiogram and x-ray firstly raise the physician's suspicion for CTEPH. One relevant finding in the patient's history is the condition of acute PE which was treated with proper anticoagulation therapy for 3 to 6 months after the initial event or the presence of other predisposing factors (as described in table 1). According to the 2022 guidelines, a CTEPH must be suspected by the time of an acute PE when suspicious radiological signs are present in the chest x-ray and when the estimated systolic pulmonary artery pressure in the echocardiogram exceeds 60 mmHg. (36) In the electrocardiogram p-pulmonary, a right bundle branch block, abnormalities in the T-wave in the chest leads as well as right-axis deviation hint to right heart strain. In chest x-ray a prominent right heart enlargement, a dilated pulmonary artery and furthermore signs of previous infarction and areas of hypoperfusion (Hampton and Westermark signs respectively) could also indicate CTEPH. With dyspnoea being the dominant symptom, patients undergo pulmonary functional tests, which in CTEPH will display a reduced transfer factor for carbon monoxide. Other signs in clinical examination are central sleep apnoea and Cheyne-Stokes respiration. (59)

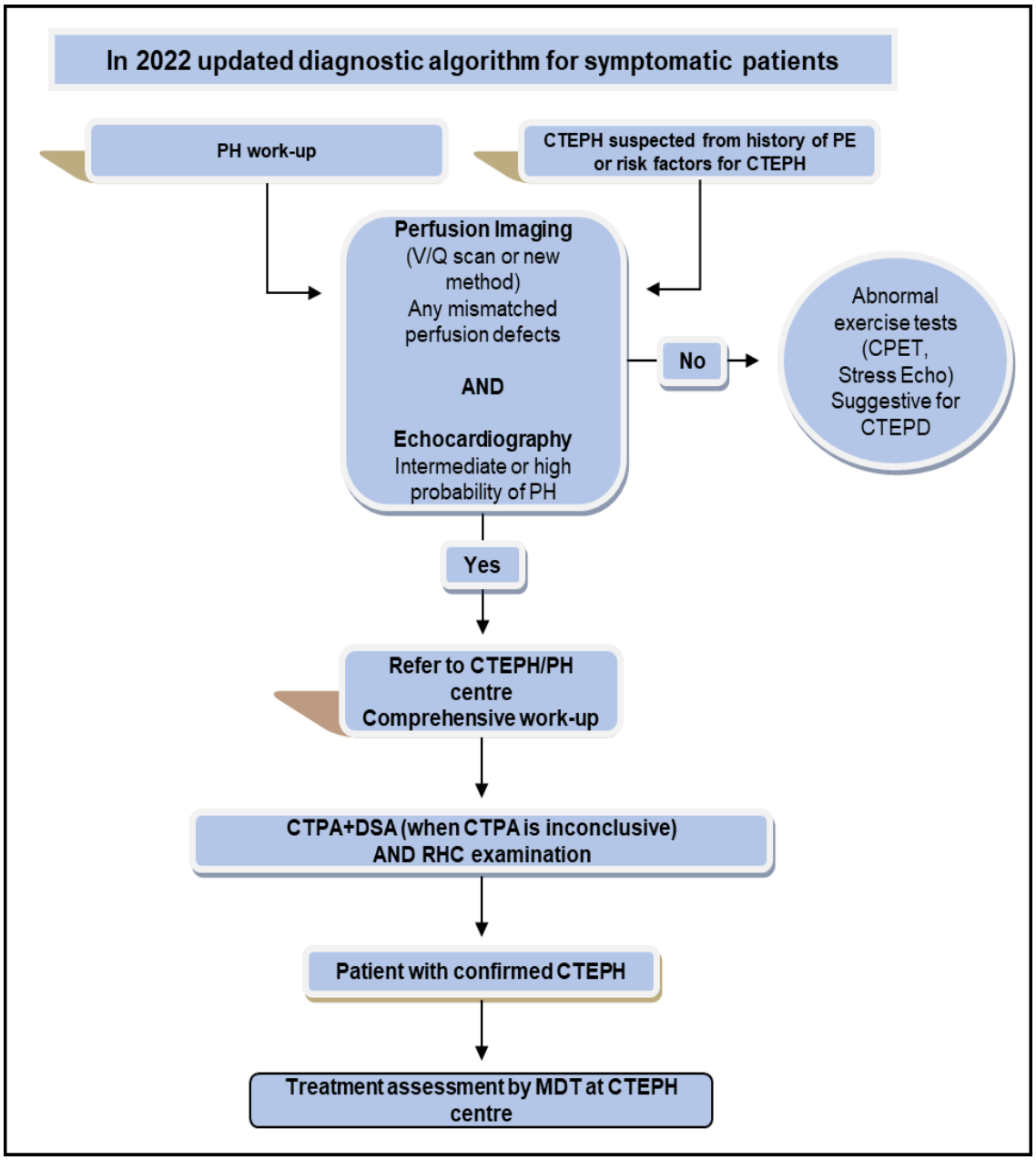

Figure 1: CTEPH Diagnostic algorithm modified by ESC/ERS guidelines 2022. (36) CTEPH: chronic thromboembolic pulmonary hypertension, PH: pulmonary hypertension, PE: pulmonary embolism, V/Q: Ventilation/Perfusion, CPET: cardiopulmonary exercise testing, CTEPD: chronic thromboembolic pulmonary disease, CTPA: computed tomography pulmonary angiography, DSA: digital subtraction angiography, RHC: right heart catheter, MDT: multidisciplinary team.

According to the in 2022 updated algorithm (36), transthoracic echocardiography (TTE) along with a ventilation/perfusion scan are the first diagnostic screening tools performed in patients presenting with symptoms, comorbidities or history implying PH. During TTE examination tricuspid regurgitation pressure gradient, right atrial and right ventricular dilatation, D-shaping of the left ventricle, reduced right ventricle contractility and doppler flow abnormalities in the right ventricular outflow tract are recommended for screening of PH.

Once the echocardiographic signs imply a high probability of PH, further imaging diagnostic as well as functional assessment tests need to be performed.

Following TTE, patients with intermediate or high probability of CTEPH directly undergo a ventilation/perfusion scan, while by patients with low probability of CTEPH a cardiopulmonary exercise testing (CPET) is recommended as a first step. During CPET, typical findings of CTEPH are ineffective ventilation and elevated alveolar-capillary gradients of oxygen and carbon dioxide due to pulmonary vascular obstruction. In these cases, patients will also undergo a ventilation/perfusion scintigraphy. The latter is a low radiation examination with a sensitivity of 96%. Therefore, with a negative V/Q scan CTEPH diagnosis can be excluded. Once the V/Q scan is positive the patient must be referred to a CTEPH specialty centre, where further diagnostic examinations will take place for final diagnosis of CTEPH. With the support of the complementary special imaging and interventional diagnostic procedures, more specifically right heart catheter (RHC) examination, the therapeutic strategy is determined.

When there is no sign of PH in echocardiography, the patients undergo a cardiopulmonary exercise testing (CPET). When V/Q is negative CTEPD is excluded. In CTEPH, CPET discloses ineffective ventilation with elevated alveolar–capillary gradients of oxygen and carbon dioxide. A typical pattern including low end-tidal carbon dioxide tension ($P_{ET}CO_{2)}$, high minute ventilation to volume of exhaled carbon dioxide (VE/VCO_2), low oxygen pulse (oxygen uptake at a given heart rate: VO_2/HR), and low peak oxygen uptake (VO_2). (21, 36)

The diagnostic procedures conducted in the CTEPH specialty centre, in accordance with ESC/ERS Guidelines for diagnosis and treatment of PH, are as following (36):

1. Computed Tomography Pulmonary Angiography (CTPA), which is an established imaging examination to confirm acute PE. Noteworthy, a negative CTPA alone cannot exclude CTEPH diagnosis. CTPA does however depict complications of the disease regarding the grade of pulmonary artery dilatation, a direct compression of the left coronary artery and hypertrophy of the bronchial arteries that can be the cause of haemoptysis. Further, CTPA contributes to the differential diagnosis by visualising more details in the mediastinal area, lung parenchyma and collateralisation(59).

It has a high sensitivity and specificity in detecting thromboembolic changes at the lobar and segmental level.

In table 3 the most characteristic findings that contribute to (differential) diagnosis are listed and divided in three categories regarding localisation.

Local vascular	Systemic vascular	Parenchymal
- Complete obstruction - Partial filling effects - Organised emboli - Intravascular bands and webs - Poststenotic dilatation - Calcifications	- Enlargement of central pulmonary vessels - Enlargement and hypertrophy of right ventricle - Pericardial effusion - Enlargement of bronchial arteries - Enlargement of neighbouring vessels (intercostal veins and arteries, mammary artery)	- Mosaic pattern (Sharp borders or unspecific - Pulmonary infarctions (irregular, linear, wedge like form, near pleura scars) - Bronchial dilatation or ipsilateral bronchiectasis (Correlation of its localisation with position of the affected vessels)

Table 5: Typical characteristics in CTPA indicating CTEPH. Modified by Opitz et al. (59)

2. **Digital subtraction angiography (DSA)** is an invasive examination which is nowadays the gold standard for assessing the pulmonary vessels. It is considered the determining projection as it displays the pulmonary arterial tree in detail. It discloses pulmonary artery branch occlusions, pouch defects, thrombus aligning the vascular wall, intravascular bands, web-filling defects and abrupt vessel tapering. (5) The pulmonary angiography not only confirms the final CTEPH diagnosis but is a helpful tool used by the PEA specialists to choose the more appropriate interventional treatment of each individual patient. PA angiogram is extremely useful for planning interventional treatments in CTEPH and has had a renaissance although it had been challenged due to its invasivity in combination with the arising of new non-invasive methods with higher sensitivity. (21)
3. **High resolution CT scan of the chest**, which can reveal the pathologies and demonstrate a mosaic pattern, a phenomenon often observed in CTEPH. However, this pattern also appears in CT scans of up to 12% of patients with PH, thus limiting its validity regarding CTEPH. (22) As mentioned in the 2022 ESC/ERS guidelines for diagnosis and treatment of PH, the combination of a pulmonary artery diameter greater or equal to 30 mm, a right ventricular outflow tract wall thickness greater or equal to 6 mm and septal deviation ≥ 140° [or RV:LV ratio ≥1]) is highly indicative of PH.
4. **Magnetic resonance imaging (MRI)** is the standard examination to assess right heart function and lung perfusion. It can disclose perfusion defects in a wedge form considered to be typical for CTEPH. With the evolution of MRI, haemodynamic of the pulmonary and systematic vasculature can be estimated. (80)
5. **Right heart catheter (RHC) examination**, an invasive examination that is crucial not only for the establishment of the diagnosis but also for the preoperative measurement of PAP and most importantly PVR. It is an essential tool for risk stratification and estimation of the prognosis of the disease.

During RHC examination a balloon flotation catheter - most commonly a modified Swan Ganz catheter (19) for pressure measurements and blood sampling including a thermistor for CO measurement via thermodilution - is inserted through the internal jugular or femoral vein into the right atrium. By inflation of the balloon, the catheter follows the blood flow towards the main pulmonary artery. Once in pulmonary artery a slightly further advance of the catheter helps obtain the pulmonary capillary wedge pressure (PCWP) and after that the balloon is deflated to avoid accidental vessel rupture. A parallel ECG monitoring ensures the correct timing of pressure measurements with ECG traces. (11)

Parameters that can be measured through the RHC are:

i. Oxygen saturation in blood samples from superior vena cava and main pulmonary artery. In the case of a difference greater than 8%, indicating a left to right shunt, further blood sampling in different locations is performed to precisely determine the location of the shunt.
ii. Cardiac output and cardiac index via Fick or thermodilution method
iii. Pressures of pulmonary artery, PCWP, right atrium and right ventricle
iv. Pulmonary and systemic vascular resistance

A mPAP ≥ 20 mmHg and a PCWP ≤ 15mmHg along with a PVR ≥ 2 Wood Units confirm the diagnosis of precapillary PH. (36)

1.2.1 Therapeutic options and prognosis

Once the final diagnosis of CTEPH is made, the challenge of deciding on the appropriate treatment option for every patient emerges. Until this date, the only established curative treatment of CTEPH is the pulmonary endarterectomy (PEA). Unfortunately, not every patient is eligible for surgical treatment. The alternative options are balloon pulmonary angioplasty and pharmacological treatment in patients with inoperable CTEPH.

1.2.1.1 Surgical treatment

The surgical removal of the thrombotic occlusion material from the pulmonary artery – PEA – is considered as the only possible curative treatment of CTEPH (as described in detail under 1.2). It is a very challenging surgery that demands high expertise surgical level, a specialised and experienced surgeon, experienced anaesthesiologists, intensive care physicians, perfusionists and specialized nurses and therefore an experienced CTEPH centre. It has been shown that the level of expertise of the centre conducting PEAs, expressed in number of patients treated per year, affects the postoperative outcome. More specifically a perioperative in-hospital mortality of 7.4% in centres performing 1-10 PEAs per year sinks to 4.7% in centres performing up to 50 PEAs per year and 3.5% in those performing over 50 procedures per year. (51) An expert centre is characterised by a high volume of PEA surgeries conducted annually (> 50 cases), a perioperative mortality under 3% as well as the ability of the surgical team to perform segmental endarterectomy. (43)

The surgery is mainly indicated for patients with central-type disease extended to the main pulmonary, interlobar and segmental arteries with the mural thrombus causing hyperplasia of the intima.

The eligibility for surgical treatment of CTEPH along with the risk stratification is defined by qualified specialists in the PEA centre and is not only dependent on the individual disease and patient characteristics but also on the experience and capability of the surgical team. Therefore, a patient that is disqualified for surgery by one specialty centre might be recommended to seek a second opinion in a different PEA centre.

The individual characteristics that are taken into consideration to assess the benefit and possibility of PEA surgery can be divided in two categories (6):

1. **Anatomical extension of the disease**; more specifically the extent of microvascular disease, risk for insufficient postoperative decrease in PVR and pulmonary pressure and finally whether the removal of the thromboembolic material is technically possible. Thrombus can easily be removed up to the segmental artery level while its presence distal of the segmental level makes its removal rather impossible or at least of much higher risk.
2. **Patient´s condition and comorbidities**. The presence of extended lung parenchymal disease may be a contraindication for surgery as the V/Q mismatch is not expected to significantly improve postoperatively. In these patients the risk-benefit evaluation leans more towards the risk than benefit side. In contrary, patients with no pathological PVR at rest and a predominant PVR increase in exercise are good candidates for surgical treatment as they are expected to improve significantly after the surgery.

The latest data indicate a rather small number of patients that are completely ineligible for surgery, emphasizing on an individualised decision-making process for each patient by a multidisciplinary team in an expert centre. (44, 51)

1.2.1.2 Interventional treatment

A total of 20 to 40 % of patients diagnosed with CTEPH are declared inoperable at the time of diagnosis mainly due to distal disease and/or comorbidities that negatively affect the chance of survival. In these patients, balloon pulmonary angioplasty (BPA) is recommended as a rescue therapy option. (36)

The indications of BPA include (61):

i. Difficulty in conducting PEA (lesion below the regional artery, difficult to approach surgically, cases of residual or recurrent PH after PEA)
ii. Insufficient response to medical treatment
iii. Patient’s preference to undergo BPA
iv. Severe multiorgan failure especially renal dysfunction and
v. Persistent symptomatic CTEPH after PEA.

During BPA, a balloon catheter is inserted through a 6-F percutaneous sheath and dilates the stenotic or occluded pulmonary lesions. Balloon size is determined via angiography and varies between a diameter of 1mm up to 6 mm. A BPA intervention is repeated every 1 to 3 months to allow the remodelling of the pulmonary vasculature and the improvement of pulmonary hemodynamic. The number of interventions on a single patient varies from 1 to 10. After implementation in 2001, in its early stages BPA was accompanied by a high complication and mortality rate (periprocedural 30-day mortality up to 5.5% as well as complication rate of 61% for vascular injury and 17% need for mechanical ventilation). Typical complications of the procedure are: vascular injuries (pulmonary vascular dissection or perforation) up to pulmonary haemorrhage, haemoptysis, temporary arrhythmias and reperfusion oedema. (75) However, as the procedure has been improved throughout the years, the mortality rates are comparable to PEA when performed in high experienced centres. (48, 83)

1.2.1.3 Pharmacological treatment

Medical treatment is indicated in inoperable patients and in patients with persistent or recurrent PH after BPA or PEA. Life-long anticoagulation with vitamin K antagonists or direct oral anticoagulants (DOACs) is indicated in all CTEPH patients. In case of hypoxaemia, shortness of breath and dyspnoea diuretics and oxygen therapy can be applied. Recently, a group of drugs (including phosphodiesterase-5 inhibitors, endothelin receptor antagonists and prostanoids) with pulmonary vasodilatory effect targeting the endothelin, nitric oxide and prostacyclin pathways has gained focus. However, until today the soluble guanylate cyclase (sGC) stimulator Riociguat along with Treprostinil are the only PAH drugs approved for treatment of inoperable CTEPH patients. (16, 36) In the last years, Riociguat has also been sparsely used as bridge to surgical therapy with clinical results being inconclusive and of little power. (60) The CHEST-1 and CHEST-2 clinical trials that studied the outcome of Riociguat therapy showed a 2-year survival of 93% and a symptom free 2-year survival of 82%. (20)

1.2.1.4 Multimodal therapy

The complexity and variability of CTEPH patients and pulmonary haemodynamic has led to the development of multimodal therapy concepts including medical and surgical treatment strategies as well as hybrid operations combining BPA and PEA. (41) While these individualized treatment concepts have improved outcome in CTEPH patients, PEA remains the gold-standard and only possible curative treatment option.

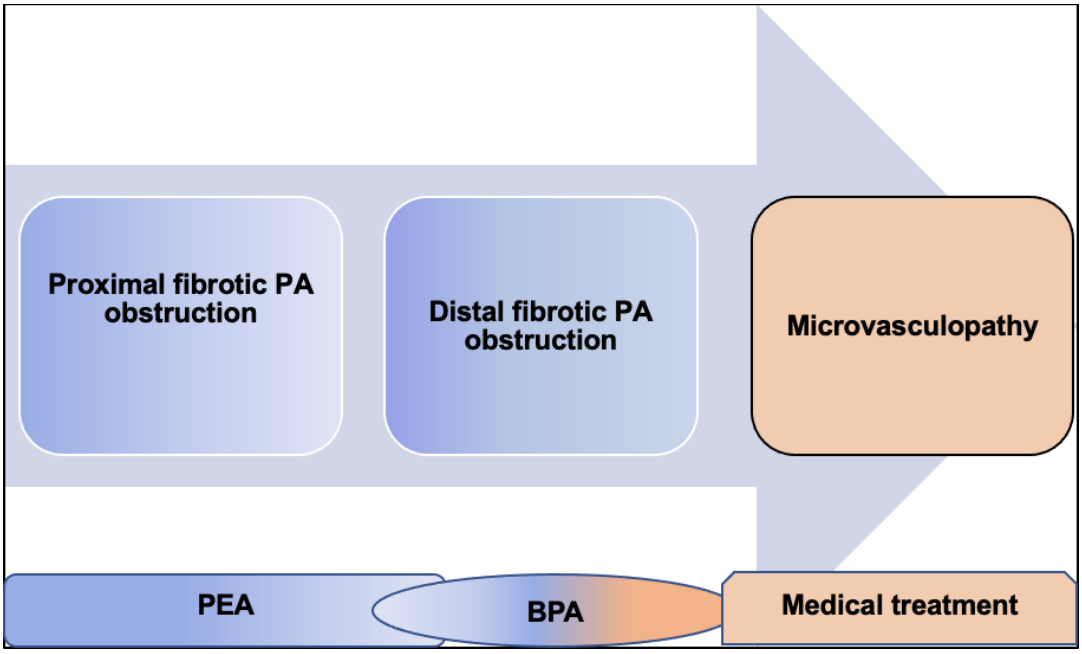

Figure 2: Therapeutic options based on obstruction localisation (modified by Guth et al. (27)). BPA: balloon pulmonary angioplasty, PA: pulmonary artery, PEA: pulmonary endarterectomy

1.3 Pulmonary Endarterectomy (PEA)

1.3.1 How it all began

Pulmonary endarterectomy evolved parallel with the recognition of chronic thromboembolic obstruction of the pulmonary arteries as a separate clinical entity. It took over 100 years from the description of PE in 1819 to 1928 when the chronic occlusion of pulmonary arteries was described. And another 28 years until the condition of chronic occlusion was described as a syndrome in 1956. In 1908 the first operative approach of pulmonary embolectomy was performed. This procedure was performed to operatively treat an acute PE and though it was unsuccessful marked the starting point in development of surgical treatment of CTEPH. The first successful pulmonary embolectomy was performed in 1924 in Europe and in 1958 in the USA. The operation was named “Trendelenburg operation“. In 1956 endarterectomy was suggested as a method to surgically treat the condition of chronic occlusion of the pulmonary arteries. In 1957 the first endarterectomy was performed; however, unsuccessful. The first successful PEA was performed in 1958 and from that point started to evolve to its modern form.

The perioperative mortality has significantly decreased as the number of conducted procedures increased; from a mortality greater than 20% in less than 250 patients operated over a thirty-year period until 1989. A to only 5% perioperative mortality achieved in 1500 patients operated between 1990 and 2002 at the University of California, San Diego (USCD). After over 30 years of experience the UCSD established the basic surgical principles for PEA. These included median sternotomy for surgical approach, application of hypothermic circulatory arrest and bilateral operation. In addition, emphasis was placed on the patient selection and on specification of markers for operability. (37)

Until today UCSD remains the leading program for PEA whose success and experience are not only used as a benchmark for centres worldwide, but their knowledge about this procedure has also been exchanged through an international databank and specialists on CTEPH and PEA congresses.

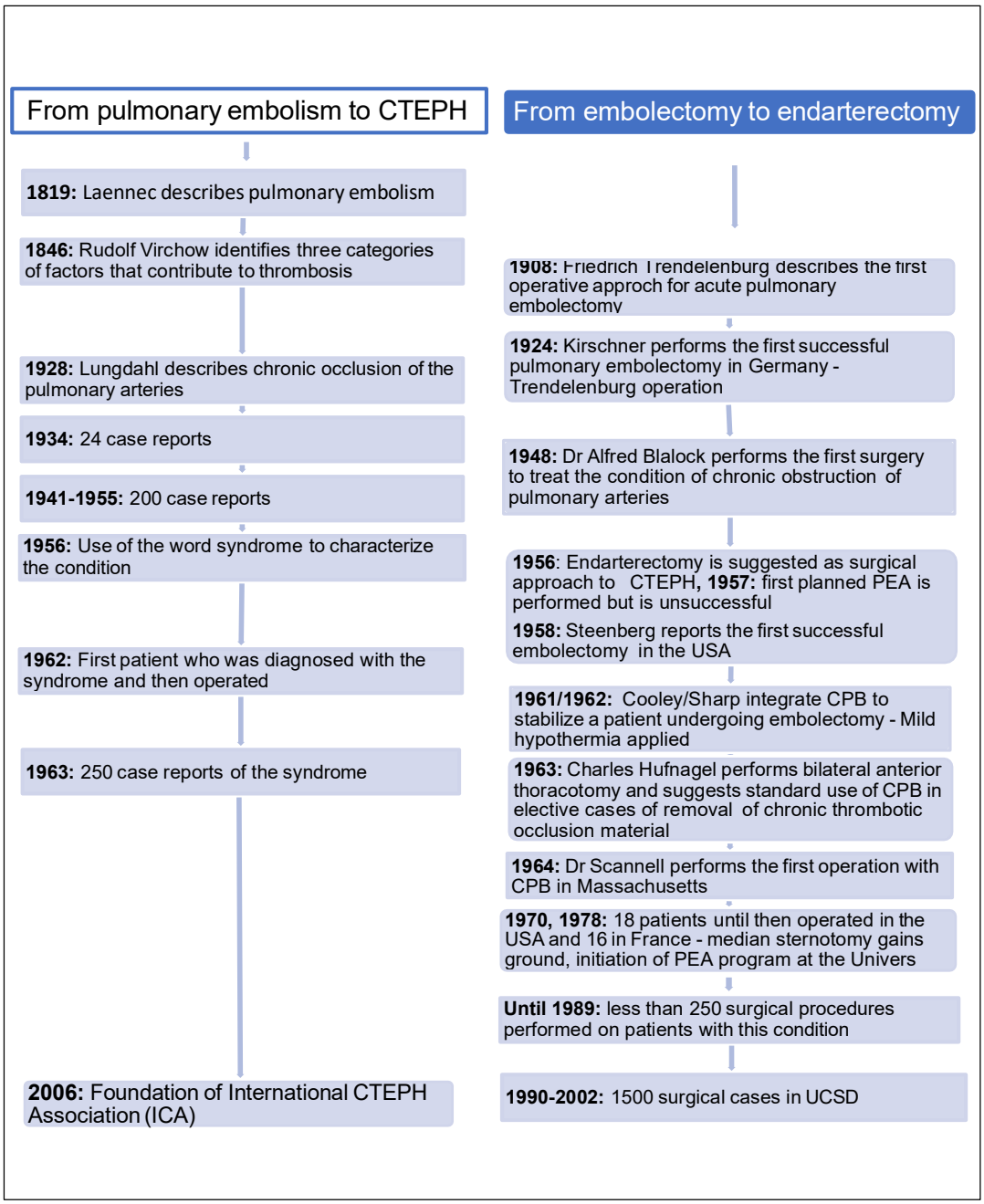

Figure 3: Historical landmarks of the evolution of PEA.

1.3.2 Perioperative management of pulmonary endarterectomy

PEA is a procedure of high complexity but has developed through years of experience an exceptionally standardized approach. Further, in recent years special surgical instruments such as double-action forceps, micro-endarterectomy spatula and PEA suction/dissectors in straight and angled shapes, have been constructed. (25)

Despite a highly standardized approach, surgical procedure, anaesthesia, perioperative haemodynamic monitoring and postoperative management slightly varies depending on the specialized centre. Therefore, the standardized operating procedures at the Kerckhoff Clinic Bad Nauheim are described below.

Under general anaesthesia and in supine position, a median sternotomy is performed. Extracorporeal circulation is achieved by cannulation of the ascending aorta and bicaval crosswise cannulation of the superior and inferior vena cava via pericardiotomy. Vent catheters are placed in the aortic root, the pulmonary trunk and into the left atrium. Afterwards, a systemically gradual uniform cooling, with a core temperature of 18°C to 20°C is implemented via the heart-lung machine. This deep hypothermia allows intervals of deep hypothermic cardiac arrest (DHCA) during PEA. DHCA is not only necessary for optimal visualization for removal of bilateral organised thrombotic material, but also for neuroprotection. Duration of DHCA is limited to short periods (in most centres 20 minutes on each side) to prevent further irreversible organ failure. In technically challenging cases, several intervals of DHCA are needed for bilateral endarterectomy. By right arteriotomy the surgeon identifies the endarterectomy field and progressively dissects distally to remove the thrombotic material. It is crucial to correctly identify the endarterectomy plane because too deep removal can lead to pulmonary bleeding while too shallow removal leads to inadequate dissection of thrombotic material. The primary goal is to remove the intima layer of the vessel, while the dissection plane may be extended to the medial layer when a high fragility of the intima layer is present. Unfortunately, this tissue quality cannot be predicted by any preoperative examinations making the procedure challenging. When endarterectomy is performed successfully, a pearly white smooth vessel wall can be visualised, the arteriotomy is closed and the surgeon proceeds to the other side. Between the intervention on each side, bypass is resumed, and the patient is reperfused. Once all accessible thromboembolic material has been removed, the left arteriotomy is closed and the patient is slowly warmed via the heart lung machine. When the patient reaches a core temperature of 32°C, a bronchoscopy is performed to exclude any minor or major pulmonary bleeding. After reaching normothermic core temperature values the patient is taken off cardiopulmonary bypass. To ensure normo- to mild hypocapnia and normoxaemia a standardized ventilation is applied, employing a pressure-controlled ventilation with a positive end-expiratory pressure (PEEP) of 10 cmH_2O. Once the surgical incision is closed the patient is transferred to the intensive care unit (ICU).

The perioperative haemodynamic monitoring of the PEA patient includes, besides the standard anaesthesiologic monitoring (ECG, pulse oximetry, NIBP), invasive arterial pressure monitoring, placement of a pulmonary artery catheter, transoesophageal echocardiography, urine output, cerebral oximetry, monitoring of depth of anaesthesia and measurement of core body temperature via nasopharyngeal and urinary bladder catheter. The pulmonary artery catheter (PAC) is placed by the anaesthesiologist for measurement of pulmonary artery pressures (pulmonary artery systolic pressure-sPAP, pulmonary artery mean pressure- mPAP, pulmonary artery diastolic pressure-dPAP) as well as cardiac output (CO), systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) after induction of anaesthesia but before performance of PEA. After the procedure and before closing of the arteriotomy, the catheter is replaced into the pulmonary artery under visualization by the surgeons. All the above-mentioned measurements are repeated at the end of PEA and in almost all cases a significant decline in pulmonary pressures is detected. The PAC is left in place and used to monitor the haemodynamic status of the patient in the ICU until successful weaning from the ventilator.

After the patient has been transferred to the ICU a standardized weaning protocol is applied, including gradual reduction of PEEP and peak inspiratory pressure. Low-dose heparin therapy is started shortly after arrival on the ICU under close coagulation and bleeding monitoring to prevent re-thrombosis but also pulmonary haemorrhage. Further, restrictive volume management is applied to lower the risk of reperfusion pulmonary oedema, one of the most severe complications after PEA. In case of this complication or persistent postoperative haemorrhage veno-venous extracorporeal membrane oxygenation (VV-ECMO) therapy may be necessary until the bleeding is controlled, the reperfusion oedema recesses and the lungs recover and adjust to the new physiological status. (71)

1.4 Corona Virus Disease-19 pandemic

1.4.1 COVID-19 worldwide

At the end of 2019 and at the dawn of 2020 humanity and medicine faced a new disease that would prove to be one of the biggest medical and health system challenges in the recent years - known as the corona virus disease 19 (COVID-19). The potentially lethal virus responsible for the pandemic is a positive-sense single-stranded RNA virus, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which originated in Wuhan, China in early December 2019. On December 29th 2019 the disease caused by SARS-CoV-2 was named COVID-19. Due to the virus' and its early appearing variants' high transmissibility and infectivity, COVID-19 was declared a pandemic on March 11th 2020(73). The pandemic was officially declared over on July 31st 2021 and with a total of over 196 million confirmed cases and over 4 million deaths, COVID-19 earned a place among the most lethal pandemics in human history.

As an effort to restrain the uncontrolled spread of the virus, the WHO recommended the governments worldwide to implement a lockdown-based crisis management. This included measures to limit the human-to-human transmission of the virus and to re-assign every available public or private capacity to scale up the public health system as quickly as possible in order to detect, isolate and treat every confirmed case. At the same time, governments were challenged to give the health system the needed support to treat patients with COVID-19 effectively while maintaining other essential health and social services for all. Social distancing measures and movement restrictions to minimize the health risks faced by the community were implemented. (81)

Furthermore, the health care systems faced not only the challenge to limit spreading of the disease, but also to better understand COVID-19 and to provide best possible health care services to these patients. The efforts to develop a safe and effective vaccine started immediately but it took almost a year until the vaccine was approved to be injected in humans.

During this time, the SARS-CoV-2 acquired pneumonia and acute respiratory distress syndrome rapidly consumed every available resource of material, medicine, oxygen supplies and most importantly intensive care capacities. Due to the severity of the disease, many cases required intensive care therapy while being isolated. Therefore, the intensive care units had to restrain their bed capacity and reassign the beds from surgical capacities to the heavily diseased patients suffering from COVID-19. Because of the high transmissibility of the virus, a lot of health care providers primarily exposed to the virus were contaminated and thus unable to provide their services in the fight against COVID-19.

A Faust circle had started that lead to reducing the intensive care capacities and therefore putting a pause on most of the scheduled but also urgent surgeries, prolonging the waiting time for these patients.

1.4.2 COVID-19 in Germany

By the time the first case of COVID-19 was diagnosed in Germany (on January 27th, 2020), preparations to handle the approaching pandemic had already started in the country. (72) Since the disease outbreak in China, Germany's existing and well-organized health infrastructure was already mobilized. Risk assessments, guidelines for detecting infected people, mapping their contacts, planning and applying social distancing measures and also in-hospital managing of COVID-19 patients had already been issued.

Germany's national health institute (Robert Koch institute) had begun to publicly communicate the daily national and international status starting January 23rd – 4 days before the first case in Germany was even recorded. When COVID-19 started spreading in Germany around the end of February 2020 measures to restrict mass gatherings and travels were already announced. (72) In March, a total lockdown was applied. In the beginning of April, extra measures for all travellers entering the country were taken and social gatherings were even further limited. All these measures resulted in decrease of daily new cases and allowing for gradual loosening of the restrictions. In summer of 2020 two small outbreaks emerged, forcing the government to declare a second lockdown. The second massive increase of new infections in Germany aligned with the one worldwide around October 2020. (75, 76)

By end of December 2020, the first vaccines against COVID-19 were authorised, and vaccination in Germany started on December 27th, 2020, with a prioritization of medical staff, elderly patients and high-risk population. Fortunately, vaccination led to the control of the pandemic as well as reduction of the deadly course of the COVID-19 disease. (77)

Germany's health system is a system of high capacity, with the highest number of hospital beds, physicians and nurses per 1.000 people in Europe (10) and also high number of testing capacities in private and public laboratories. In March 2020 the German Association for intensive care and Robert Koch institute initiated a register, where a daily report of available ICU beds with and without ventilating capacities and ICU beds where complicated COVID-19 cases could be treated was made public. This created a network of all hospitals countrywide that helped the treating physicians properly and quickly transfer their patients. On top of that, due to the limited availability and overwhelmed health system in several other EU countries, Germany also treated international COVID-19 patients. In order to ensure the treatment of rising numbers of

COVID-19 patients, all elective surgeries were postponed beginning March 18th 2020 and a high number of ICU beds had to be reserved for COVID-19 patients. (15) These policies especially applied to hospitals where ECMO therapy was available, such as PEA centres, considering a high number of COVID-19 patients needed ECMO treatment to survive. Thus, especially during the two big surges of the pandemic, the health care system of Germany was strained and a lot of elective surgery cases had to be postponed leading to prolonged waiting time also for CTEPH patients. (78, 79)

1.5 Aim of the study

Although CTEPH is considered to be a potentially lethal disease, PEA is an elective surgery that had to be postponed during COVID-19 pandemic, especially considering all patients after PEA need an ICU bed. Therefore, the aim of this study is to analyse the impact of the COVID-19 pandemic on the duration from CTEPH diagnosis to operative treatment and furthermore to analyse whether this waiting time was associated with inferior postoperative outcome and/or with worsening of preoperative haemodynamic status.

2 Material and methods

2.1 Study design

A retrospective single centre observational study was conducted at the Kerckhoff Clinic in Bad Nauheim, Germany. The Kerckhoff Heart and Lung centre is a high-volume specialized centre for CTEPH patients that conducts > 150 PEAs per year. The surgical team has performed over 3000 surgeries since its foundation in 1989. The retrospective study was approved by the ethics committee of the Justus Liebig University Giessen (amendment number: 199/15). The study was carried out in accordance with the declaration of Helsinki.

2.1.1 Study population, inclusion and exclusion criteria

The patient population consisted of a total of consecutive 436 patients with confirmed CTEPH diagnosis according to the 2015 ESC/ERS Guidelines for the diagnosis and treatment of PH that underwent PEA at the Kerckhoff Clinic Bad Nauheim during the period from March 1st, 2018 to December 31st, 2019 and March 1st, 2020 to December 31st, 2021. We followed the same guidelines used to set the diagnosis and guide the treatment at the time of surgery. According to the guidelines from 2015 the criteria for CTEPH diagnosis were: mPAP≥25mmHg, PAWP≤15mmHg, mismatched V/Q lung defects and specific diagnostic signs seen in CT angiography, MRI or pulmonary angiography, at least 3 months of effective anticoagulation after PE. (17)

To investigate a possible association between waiting time from diagnosis to surgical treatment during the COVID-19 pandemic, the patient population was divided into a pre-pandemic and pandemic period.

Patients included into the pandemic group were operated on between March 2020 and December 2021. While the first case of SARS-CoV-2 infection in Germany was reported on January 27th, 2020, the first lockdown in Germany was announced in March 2020 which was followed by the delay of scheduled operations, like PEAs. Hence, the beginning of the pandemic period for the study population was set starting March 1st, 2020. Although the COVID-19 pandemic was officially declared over on July 31st, 2021, the number of patients waiting on PEA surgery was already increased. On top of that, a fourth pandemic wave occurred until the end of 2021, leading to the decision to prolong the pandemic period until December 31st, 2020, for the purposes of this study. Therefore, the end of the pandemic-period of the study population was conventionally set on December 31st, 2021.

In order to keep the time periods equal in length, the non-pandemic period included patients operated from March 2018 till 31st of December 2019.The inclusion and exclusion criteria are listed in tables 5 and 6 respectively.

Age > 18 years
Surgical Procedure: Pulmonary endarterectomy
Pre-Pandemic Period: 01.03.2018 – 31.12.2020
Pandemic Period: 01.03.2020 – 31.12.2021
Documented CTEPH diagnosis via RHC examination according to the ESC/ERS Guidelines 2015
Documented time of decision for PEA by specialty consulting team and / or by date of angiography
Documented preoperative hemodynamic values via RHC and perioperative hemodynamic values via PAC

Table 6: Inclusion criteria. CTEPH: chronic thromboembolic pulmonary hypertension, ESC/ERS: European respiratory society/European society of cardiology, PAC: pulmonary artery catheter, PEA: pulmonary endarterectomy, RHC: right heart catheter

Age < 18 years
Missing data regarding time of diagnosis, time of decision for PEA, pre- and peri-operative hemodynamic data
Intraoperative diagnosis of pulmonary sarcoma
Chronic thromboembolic disease (CTED) without diagnosis of pulmonary hypertension

Table 7: Exclusion criteria. CTED: chronic thromboembolic disease, PEA: pulmonary endarterectomy

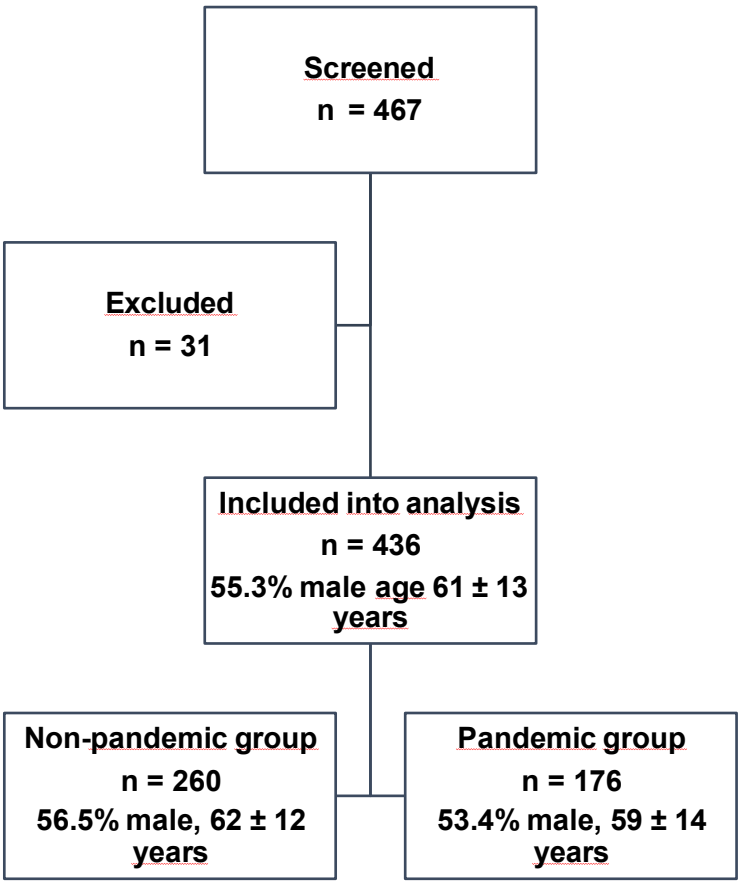

Figure 4: Screening process flow chart

2.1.2 Data collection

Data collection was achieved by studying the digital patient files. They included documentation of patients' characteristics, comorbidities and diagnostic examinations. The parameters collected for assessment were as following:

(1) Patient characteristics: Patient's sex, age, height, weight and body mass index (BMI) at the time of operation

(2) Disease characteristics:

(i) WHO Functional class at the time of operation describing the severity of symptoms suffered by patients with pulmonary hypertension (see tab.3).

(ii) Long-time oxygen therapy

(3) Haemodynamic parameters:

The pulmonary haemodynamic values included systolic, mean and diastolic pulmonary pressure and PVR. While systolic and diastolic pulmonary artery pressures can be measured via pulmonary artery catheter, mean pulmonary artery pressure (mPAP) is a calculated value derived using the following equation:

$$\mathbf{mPAP = 2/3x(dPAP)+1/3x(sPAP)}$$

PVR is the resistance against blood flow from the 4 pulmonary veins of the lungs to the left atrium. It is calculated according to Ohm's law: I=V/R (I= current, V=Voltage, R= Resistance)

$$\mathbf{PVR=80 \times (mPAP-LAP)/CO}$$

mPAP: mean pulmonary pressure, LAP: left atrial pressure, CO: cardiac output

Further measurements conducted are cardiac output and cardiac index calculated via the thermodilution method or by the Fick equation:

$$\mathbf{CO=} \frac{\dot{V}\mathbf{O2}}{\mathbf{Ca-Cv}}$$

CO: cardiac output, $\dot{V}O_2$: oxygen consumption rate (Body surface area (BSA) x 130), Ca: oxygen content of arterial blood (CaO_2 (mL O_2/dL) = (1.34 x haemoglobin concentration x SaO_2) + (0.0031 x PaO_2), SaO_2: arterial oxyhaemoglobin saturation, PaO_2: arterial oxygen tension), Cv: oxygen content of mixed venous blood (measured in the blood sample drawn from the catheter line in the pulmonary artery)

In order to measure the cardiac output via the thermodilution method, a cold saline injectate is applied at the proximal line of the PAC into the right atrium. As the injectate passes through the ventricle and into the pulmonary artery, it mixes and cools blood in the cavity. A thermistor at the catheter tip in the pulmonary artery measures the temperature of the flowing blood (compared to temperature at the start of injection) and calculates the cardiac output from the right ventricle. The procedure is repeated at least 3 times, and an average value is calculated. The cardiac output changes with respiration, therefore it is important to inject the solution at a consistent time point during the respiratory circle.

The equation used to calculate the cardiac output via the thermodilution method is a modified Stewart-Hamilton equation:

$$\mathbf{V} = \frac{\mathbf{V} \cdot (\mathbf{T_b} - \mathbf{T_i})}{\mathbf{k_1} \cdot \mathbf{k_2}}$$

(V̇): cardiac output, (V): volume, (Tb): temperature of the blood, (Ti): temperature of the injectate, (k1): "density constant," specific to the indicator and blood properties, (k2): "calibration constant," representing the temperature change corresponding to each height interval of the thermodilution curve.

These haemodynamic parameters were documented at two time points:

i. Pulmonary haemodynamics at rest via RHC examination during the diagnostic procedure. A modified Swan-Ganz catheter is placed under X-Ray control in the wedge position. It has multiple lines that can also be used to draw blood samples and measure the pressure on diverse locations from superior vena cava to the pulmonary artery along with a thermistor at the catheter tip for thermodilution method. During the diagnostic procedure the patient lies awake on the examination table and is asked to exhale and shortly hold their breath. At that time point of end-expiration the pulmonary capillary wedge pressure is measured. After this value is obtained the catheter is carefully withdrawn in the pulmonary artery where the sPAP and dPAP values are obtained. Applying the mean pulmonary artery equation on these values, mPAP value at rest is calculated. Further, applying the equation for PVR, PVR at rest is calculated. Cardiac output is calculated either with the Fick equation or with the thermodilution method.

ii. Preoperative pulmonary haemodynamic via pulmonary artery catheter (PAC). This included measurements of sPAP, dPAP and mPAP after induction of anaesthesia but before the incision. PVR and CO was calculated via the method of thermodilution. In the study centre, PCWP is as standard estimated at 10 mmHg, so that a further perioperative wedging of the PAC is avoided, which is contra-indicated at the postoperative period.

(4) Comorbidities (as documented in the list of diagnoses on the referral letter or on the letter of discharge, archived in the patients' electronic medical file):

i. Coronary vessel disease
ii. Diabetes mellitus
iii. Cerebral vascular disease
iv. Peripheral vascular disease
v. Long-time oxygen therapy preoperatively
vi. Heart failure
vii. History of splenectomy
viii. Ventriculo-atrial shunts

(5) **Length of ICU stay**. The number of days was documented as number of begun calendar days. For patients that had to be transferred to another hospital, length of ICU and hospital stay was defined as the length of stay at the study's centre.

(6) **In-hospital and 30-day mortality**

(7) **Occurrence of reperfusion oedema**: Reperfusion oedema is a common complication, with an incidence of up to 20% after PEA. The pathophysiological mechanism of its occurrence is not completely clear; however, a dysfunctional capillary-alveolar membrane in the previously occluded areas reperfused after PEA is considered the cause for reperfusion oedema. Its diagnosis is based on clinical signs – dyspnoea along with blood gas analysis and chest radiography, that show hypoxaemia and new radiological opacity in the reperfused lung areas. It usually occurs within the first 48 hours after surgery and its treatment varies from diuresis, maintenance of haematocrit and application of positive end-expiratory pressure to extracorporeal membrane oxygenation in the most severe cases. (54) The development of reperfusion oedema seems to significantly increase the length of ICU stay. (40)

(8) **Initiation of extracorporeal membrane oxygenation therapy (ECMO)** - veno-arterial (VA-ECMO) or veno-venous (VV-ECMO).

(9) **Documented major adverse cardiac events (MACE)** (acute myocardial infarction, stroke, cardiovascular death, arrhythmias).

2.1.3 Definition of primary and secondary endpoints

(1) **Main exposure:** waiting time from diagnosis to surgical treatment in weeks

i. **Documented CTEPH diagnosis time:** documented diagnosis by the PEA-specialists consulting team during PEA conference at the Kerckhoff Clinic. In case of diagnostic procedure being conducted in another CTEPH centre, the documented date of diagnosis in the referral letter was defined as the date of CTEPH diagnosis.

ii. **Documented date of decision to operate:** documented during the PEA conference where the team of specialists declared the patient as eligible for surgery. When no document of the PEA conference was found, as date of decision to operate was defined the date on which the pulmonary angiography was performed. In the few cases that the pulmonary angiography took place externally and no date was documented the date on which the specialty team sent an invitation to the patient to ask him to schedule his surgery was documented as the date of decision to operate.

iii. **Duration from CTEPH diagnosis to surgical treatment (time in weeks):** Waiting time to undergo the surgery is defined as the time (in weeks) from indication to surgical treatment to the day of surgery.

iv. **Duration between RHC examination (time in weeks):** Duration from the first RHC examination to the preoperative PAC measurements after induction of anaesthesia (time in weeks).

(2) <u>Primary endpoints:</u>

i. Pre-operative PVR and mPAP

ii. Change in PVR and mPAP between RHC examination contributing to diagnosis and PAC measurement after induction of anesthesia on the day of surgery. For the measurement of PVR at the first catheter examination we accepted values obtained with Fick equation and thermodilution. PVR measurement via PAC was obtained via the thermodilution method.

iii. Time intervals between onset of symptoms to diagnosis of CTEPH to declaration of operability and to PEA and more specifically:

a. Time interval between onset of symptoms and diagnosis
b. Time interval between diagnosis and declaration of operability
c. Time interval between diagnosis and surgery
d. Time interval between declaration of operability and surgery
e. Time interval between RHC examination contributing to diagnosis and PAC measurement after induction of anesthesia on the day of surgery

All time intervals were documented in weeks.

(3) <u>Secondary endpoints:</u>

i. Outcome parameters including in-hospital and 30-day mortality

ii. Length of ICU and hospital stay

iii. Major adverse cardiac invents (including acute myocardial infarction, stroke, or cardiovascular death and arrhythmias)

iv. Occurrence of reperfusion oedema

v. Need for veno-arterial or veno-venous extracorporeal membrane oxygenation (ECMO) therapy

2.1.4 Software

The software used for collection and statistical analysis of the data are listed in Table 8. The data was extracted from the different documentation software programs used at the Kerckhoff Clinic which is the Metavision5, the Metavision5 archive (data documented before 2019) and Kercknet+. In iMedOne further information, such as documents regarding scheduling of the operation and other medical documents sent by the referring centre, was collected. HyperPacs program was also used to determine the exact date of pulmonary angiography or CT when no date of declaration of eligibility for surgery was to be found in Kercknet+ or iMedOne.

iMedOne®	Telekom Healthcare Solutions
Metavision ® Version 5 and Kercknet+	iMDsoft
Metavision 5 Langzeitarchiv®	iMDsoft
HyperPacs® Version 8.16.0.1	ITZ Medicom GmbH &Co.KG Telemis GmbH
Microsoft Office Excel® Version 2010	Microsoft Corporation
SPSS Version 27.0	IBM, Armonk, New York USA

Table 8: Software programs used for collection and statistical analysis of the data

2.1.5 Statistical plan

We performed a descriptive data analysis and test for normal data distribution for the complete study cohort and separately for the two patient groups. In order to compare the mean values, we performed a t-test for the numerical variables and a Fishers exact (chi²-) test for the nominal/ordinal variables. By data with a skewed distribution, we calculated the median value and interquartile range. A multivariate linear regression was used to analyse the association between the different waiting times from CTEPH diagnosis/indication until PEA surgery and the change in pulmonary haemodynamic parameters (more specifically the preoperative mPAP and PVR values). The choice of co-variables was based on literature research and included known parameters that affect pulmonary haemodynamic and postoperative outcome (listed in tab.9).

Factors affecting pulmonary hemodynamic	Factors affecting postoperative outcome
Age	Age
Sex	Sex
BMI	BMI
Coronary vessel disease	Diabetes Mellitus
Heart failure	Cerebrovascular disease
COPD	Coronary vessel disease
	Chronic kidney disease
	Peripheral vascular disease
	Long-time oxygen therapy preoperative

Table 9: Choice of co-variables

A multivariate binary logistic regression model was performed to analyse the association between the duration from CTEPH diagnosis to operative treatment and occurrence of reperfusion oedema. For the remaining continuous variables, a multivariate linear regression was performed.

To analyse the impact of the COVID-19 pandemic on the duration from CTEPH diagnosis to operative treatment, the mean duration was calculated for the pre-pandemic and pandemic time. In a second step, we included COVID-19 pandemic in all multivariate analyses as an additional variable and performed sensitivity analyses for the two groups separately.

3 Results

3.1 Demographic data

The study population included a total of 436 patients: 260 (113 female vs. 147 male) in the non-pandemic vs. 176 (82 female vs. 94 male) in the pandemic group. (see Fig.4 methods part).

3.2 Patient characteristics

All patient characteristics can be found in table 10.

3.2.1 Sex, Age

There was no difference regarding sex in both groups. However, patients in the pandemic group were significantly younger than in the non-pandemic group (59 ±13.98 vs. 62 ± 12.44 years, p = 0.018).

3.2.2 Comorbidities

Regarding comorbidities we did not see any difference between both groups for obesity, coronary vessel disease or COPD. However, there were more patients diagnosed with diabetes (P: 27.3% vs. NP: 18.5%, p < 0.001), arterial hypertension (P: 57.4% vs. NP: 47.3%, p = 0.039) and heart failure (P: 2.8% vs. NP: 0%, p < 0.001) in the pandemic group. In line with the pathophysiological nature of the disease, the majority of patients in both groups had a history of pulmonary embolism (P: 96.6% vs. NP: 93.8%, ns). Further, 55.1% in the pandemic group and 57.3% of the patients in the non-pandemic group had a history of deep vein thrombosis, with no significant difference between the groups.

3.3 CTEPH specific characteristics

3.3.1 WHO classification

No significant difference was observed between the two groups regarding the WHO classification at time of diagnosis, with about 70% of the patients being classified as WHO functional class III and about 19% of the patients being classified as WHO functional IV.

3.3.2 Long-time oxygen therapy

A total of 130 patients of the study population needed long-time oxygen therapy (LTOT) at the time of surgery. The percentage of patients needing LTOT was significantly higher in the pandemic group compared to the non-pandemic group (P: 36.4% vs. NP: 25.4%, p = 0.014).

3.4 Surgical characteristics

There was no significant difference between the two groups regarding the mean duration of the surgery (P: 416.5±58.49 vs. NP: 405.8±63.06 minutes, p = 0.457). The mean duration of cardiopulmonary bypass (CPB) (P: 274.9±36.75 vs. NP: 271.74±45.08 minutes, p=0.076) and deep hypothermic cardiac arrest (DHCA) (P: 39.5±9.30 vs. NP: 38.2±10.31, p = 0.207) also not significantly longer in the pandemic group.

Patient characteristics	Study population (n=436)	Pandemic group (P) (n=176)	Non-pandemic group (NP) (n=260)	p-value
Age (in years)	61±13.2	59±14	62±12.4	0.055
Sex (female)	195 (44.7%)	82 (46.6%)	113 (42.8%)	0.519
Obesity	151 (34.6%)	64 (36.4%)	87 (33.5%)	0.532
Nicotine consumption	31 (7.1%)	8 (4.6%)	23 (8.8%)	0.085
NYHA≥3	212 (48.6%)	91 (51.7%)	121 (46.5%)	0.288
Arterial hypertension	224 (51.4%)	101 (57.4%)	123 (47.3%)	**0.039**
Diabetes	96 (22%)	48 (27.3%)	48 (18.5%)	**0.029**
Chronic kidney disease	270 (61.9%)	101 (57.4)	169 (65.0)	0.108
Coronary vessel disease	74 (17%)	34 (19.3%)	40 (15.4%)	0.283
Heart failure (HFrEF)	5 (1.1%)	5 (2.8%)	0 (0%)	**0.006**
COPD	54 (12.4%)	21 (11.9%)	33 (12.7%)	0.813
History of acute pulmonary embolism	413 (94.7%)	169 (96.6%)	244 (93.8%)	0.204
History of DVT	246 (56.4%)	97 (55.1%)	149 (57.3%)	0.652
CTEPH specific characteristics				
WHO functional class				
FC II	40 (9.2%)	14 (8.9%)	30 (11.5%)	0.456
FC III	308 (70.6%)	125 (70.3%)	200 (71.8%)	0.960
FC IV	83 (19%)	36 (20.6%)	49 (17.5%)	0.554
LTOT	130 (29.8%)	64 (36.4%)	66 (25.4%)	**0.014**
Surgical characteristics				
Duration of surgery (min)	410.1±61.4	416.5±58.5	405.8±63.1	0.457
Duration of cardiopulmonary bypass (CPB) (min	273±41.9	274.9±36.8	271.7±45.1	0.076
Duration of deep hypothermic cardiac arrest (DHCA) (min)	38.7±9.9	39.5±9.3	38.2±10.3	0.207

Table 10: All patient characteristics as well as CTEPH and surgical characteristics for the study cohort. CPB: cardiopulmonary bypass, CTEPH: chronic thromboembolic pulmonary hypertension, DHCA: deep hypothermic cardiac arrest, FC: functional class, HFrEF: heart failure with reduced ejection fraction, LTOT: long-tome oxygen therapy, WHO world health organisation

3.5 Waiting time

3.5.1 Waiting time from onset of symptoms to surgery

Overall waiting time from onset of symptoms until CTEPH diagnosis, declaration of operability and PEA surgery did not differ between the two groups as shown in Figure 5. The median time interval from onset of symptoms to diagnosis was 62.5 (IQR 40.0-125.75) weeks in the pandemic and 61.0 (IQR 26.0-143.0) weeks in the non-pandemic group (p = 0.216). The median time spent between onset of symptoms and declaration of operability was 77.0 (IQR 49.0-156.0) weeks in the pandemic vs. 65.0 (IQR 34.25-136.75) weeks in the non-pandemic group (p = 0.110). Lastly, there was no significant difference observed between the two groups regarding the median time interval between onset of symptoms to PEA surgery (P: 97.0 IQR 62.25-167.5 weeks vs. NP: 71.0 IQR 39.5-148.25 weeks, p = 0.103).

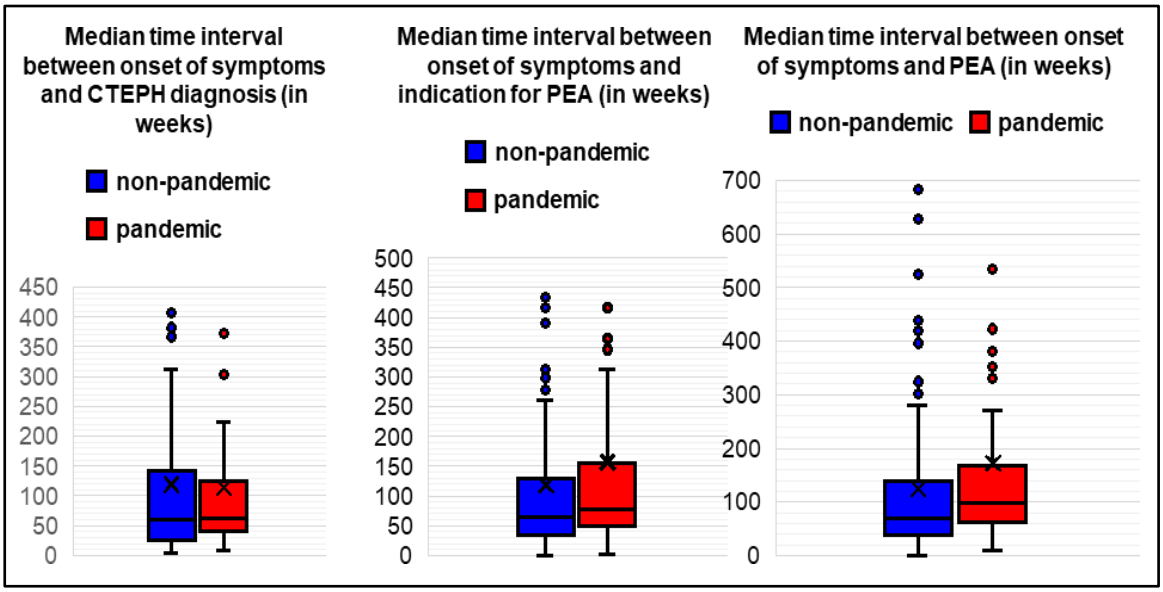

Figure 5: Median time interval from onset of symptoms till PEA between the pandemic and non-pandemic group in weeks. CTEPH: chronic thromboembolic pulmonary hypertension, PEA pulmonary endarterectomy

3.5.2 Waiting time from CTEPH diagnosis to surgery

Waiting times from CTEPH diagnosis till PEA surgery are shown in figure 6. Patients in the pandemic group had a significantly longer overall waiting time between CTEPH diagnosis and day of surgery. More specifically, the median waiting time from diagnosis to surgery was 31.0 (IQR 17.5 - 51.5) weeks in the pandemic group vs. 14.0 (IQR 6.0 - 23.0) weeks in the non-pandemic group (p < 0.001).

In the pandemic group patients the median of waiting time from diagnosis to declaration of operability was 11.5 (IQR 4.0-31.25) weeks vs. 6.0 (IQR 0.0-17.0) weeks in the non-pandemic group ($p < 0.001$). Furthermore, the median of time interval between the declaration of operability and the date of the scheduled surgery was 14.0 (IQR 7.0 - 21.25) weeks in the pandemic vs. 5.0 (IQR 2.0 - 9.0) weeks in the non-pandemic group ($p < 0.001$).

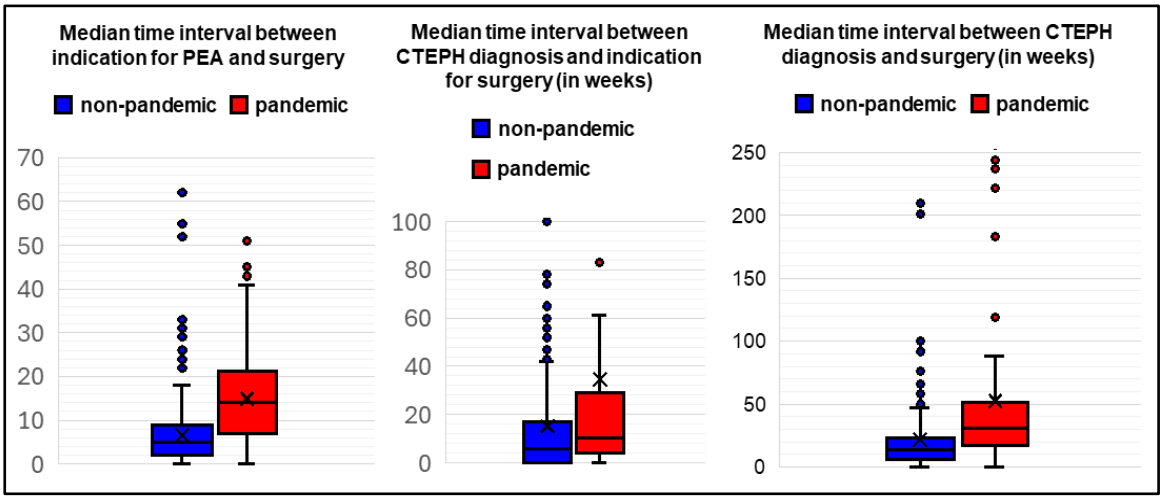

Figure 6: Median time interval from diagnosis of CTEPH to PEA between pandemic and non-pandemic group in weeks. CTEPH: chronic thromboembolic pulmonary hypertension, PEA: pulmonary endarterectomy

3.5.3 Time interval between the measurements

The time interval between the two RHC measurements was also significantly longer in the pandemic group (P: 21.0 (IQR 11.5 – 30.5) vs NP: 12.0 (IQR 5.57 – 19.0) weeks, $p = 0.005$), as shown in Figure 7.

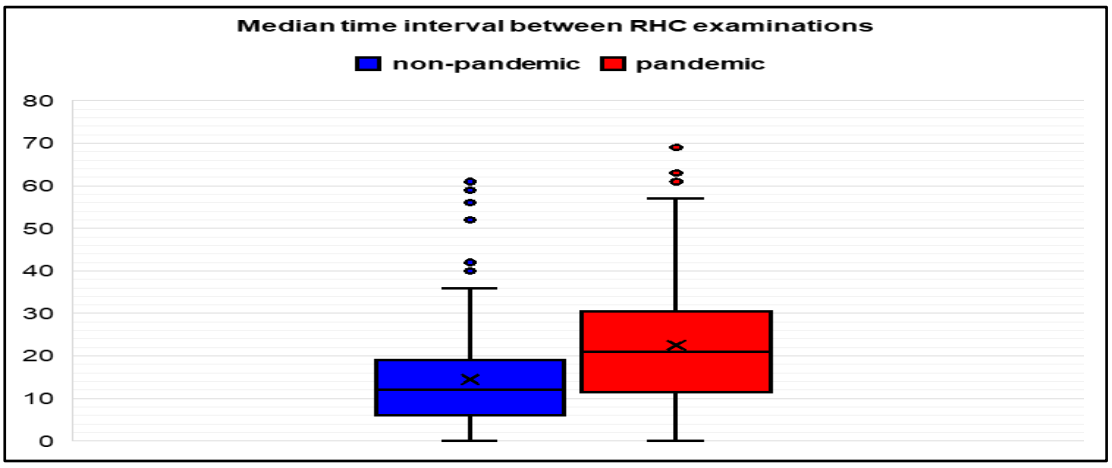

Figure 7: Median time interval from the first measurement in RHC to the measurement before surgery (in weeks). RHC: right heart catheter

3.6 Primary endpoint

All pulmonary haemodynamic values are shown in table 12. There was no statistically significant difference in PVR and mPAP between the two study groups at any time point of documentation. When looking at the change of mPAP and PVR between values at time of diagnosis and day of surgery there was also no difference between the pandemic and non-pandemic group (Fig. 8 and Fig. 9).

Hemodynamic value	Group 1 (pandemic)	Group 2 (non-pandemic)	p-value
mPAP(0)	42.8±11.08	41.6±10.43	ns
mPAP(op)	44.1±13.85	42.9±12.42	ns
PVR(0) (WU)	8.0±4.10	7.3±3.36	ns
PVR(op) (WU)	8.4±4.77	7.6±4.04	ns
mPAP difference	1.2±10.82	1.19±10.77	ns
PVR difference (WU)	0.58±3.60	0.10±3.23	ns

Table 11: Pulmonary hemodynamic in the two study groups. (mPAP(op): mean pulmonary arterial pressure at the time of surgery, mPAP(0): mean pulmonary arterial pressure at the first RHC examination, mPAP difference: mPAP(op)-mPAP(0), PVR(0): mean pulmonary vascular resistance at the first RHC examination, PVR(op): mean pulmonary vascular resistance at the time of surgery, PVR difference: PVR(op)-PVR(0), WU: Wood Units)

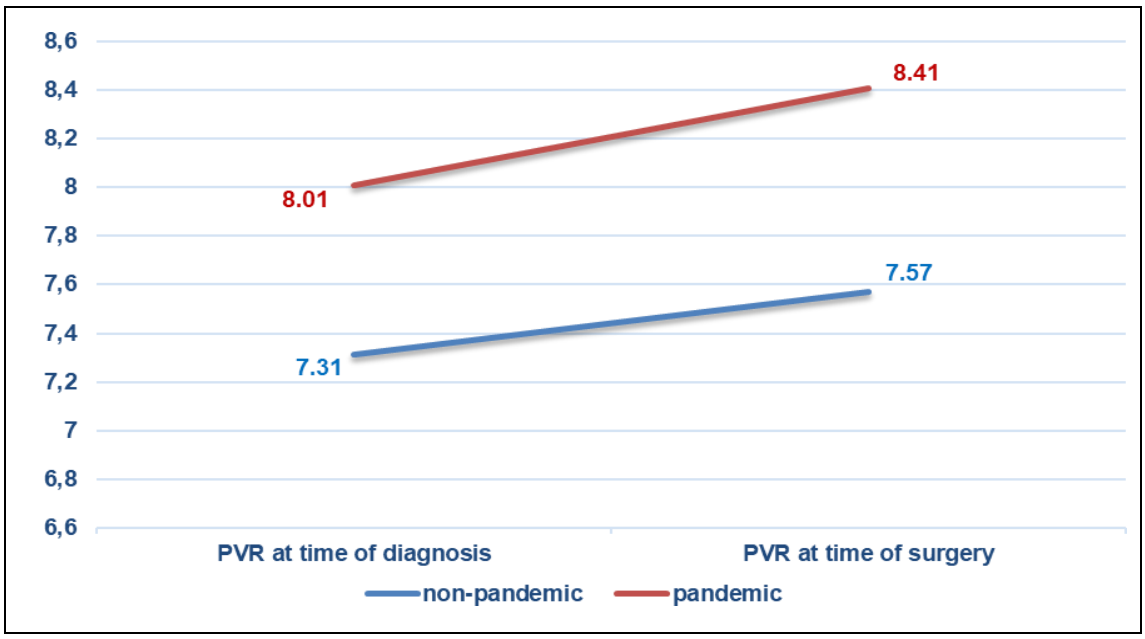

Figure 8: Change in mean PVR (in Wood Units-WU) value in the two groups from time of diagnosis to time of surgery. PVR: pulmonary vascular resistance

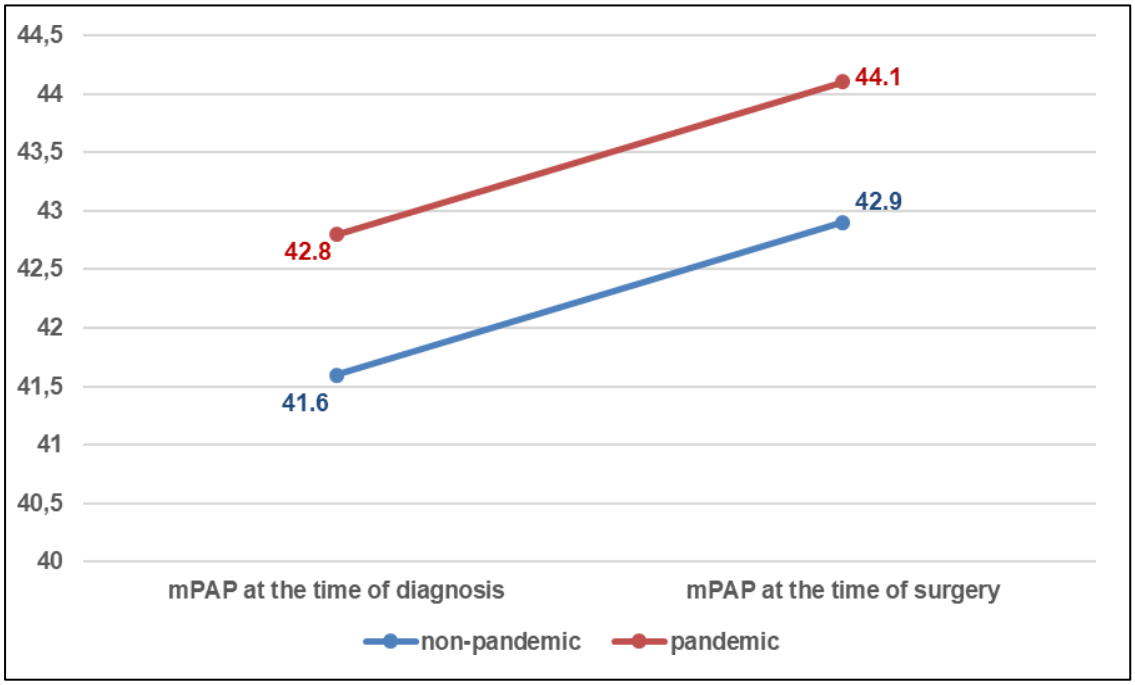

Figure 9: Change in mean mPAP (in mmHg) value in the two groups from time of diagnosis to time of surgery. mPAP: mean pulmonary artery pressure.

Further, there was no association between any of the above-mentioned waiting times and preoperative haemodynamic (see Tab.12 and Tab.13)

Variates	OR	95% CI for OR		p-value
		Lower	Upper	
Time interval between indication for PEA and PEA	-0.013	-0.306	0.279	0.928
Time interval between diagnosis and indication for PEA	-0.024	-0.077	0.029	0.371
Time interval between diagnosis and PEA	-0.025	-0.076	0.027	0.350

Table 12: Results of regression analysis of diverse time intervals and difference in mPAP from time of diagnosis to time of operation. PEA: pulmonary endarterectomy, mPAP: mean pulmonary arterial pressure

Variates	OR	95% CI for OR		p-value
		Lower	Upper	
Time interval between indication for PEA and PEA	-0.013	-0.306	0.279	0.928
Time interval between diagnosis and indication for PEA	-0.024	-0.077	0.029	0.371
Time interval between diagnosis and PEA	-0.025	-0.076	0.027	0.350

Table 13: Results of regression analysis of diverse time intervals and difference in PVR values from time of diagnosis to time of operation. PEA: pulmonary endarterectomy, PVR: pulmonary vascular resistance

3.7 Secondary endpoints

3.7.1 ICU stay

There was no significant difference regarding the length of ICU stay between the two study groups (P: 1.0 (IQR 0 - 2.00) days vs. NP: 1.0 (IQR 1.0 – 2.0) days, p = 0.173).

3.7.2 Mortality

In the study population the overall 30-day and 1-year mortality was respectively 1.4% and 2.3%. There was no significant difference observed between the study groups neither in the 30-day (P:1.1% vs. NP:1.5%, p = 0.721) nor in the 1-year mortality (P:1.7% vs. NP:2.7%, p = 0.5), as shown in Kaplan-Meier curve in Figure 10 and Figure 11.

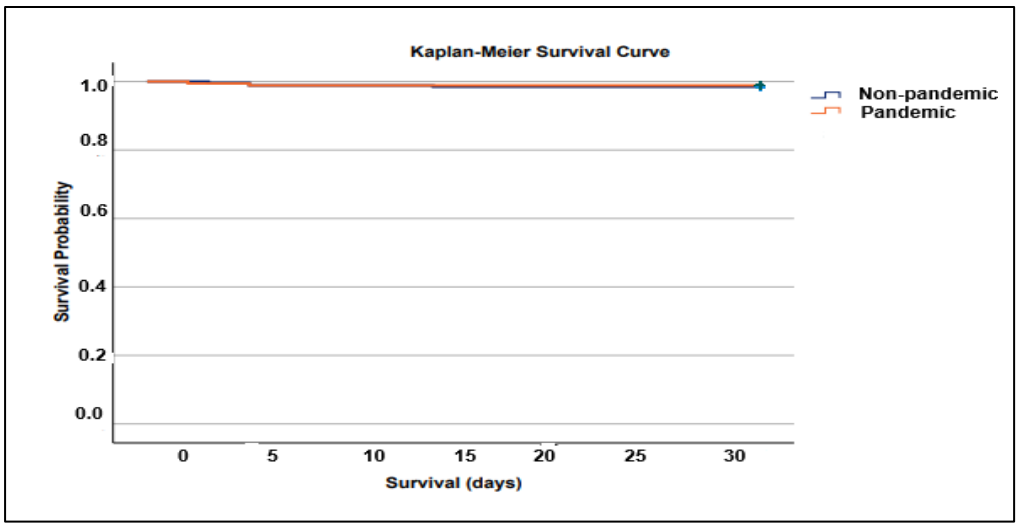

Figure 10: Kaplan-Meier curve for 30-days-survival

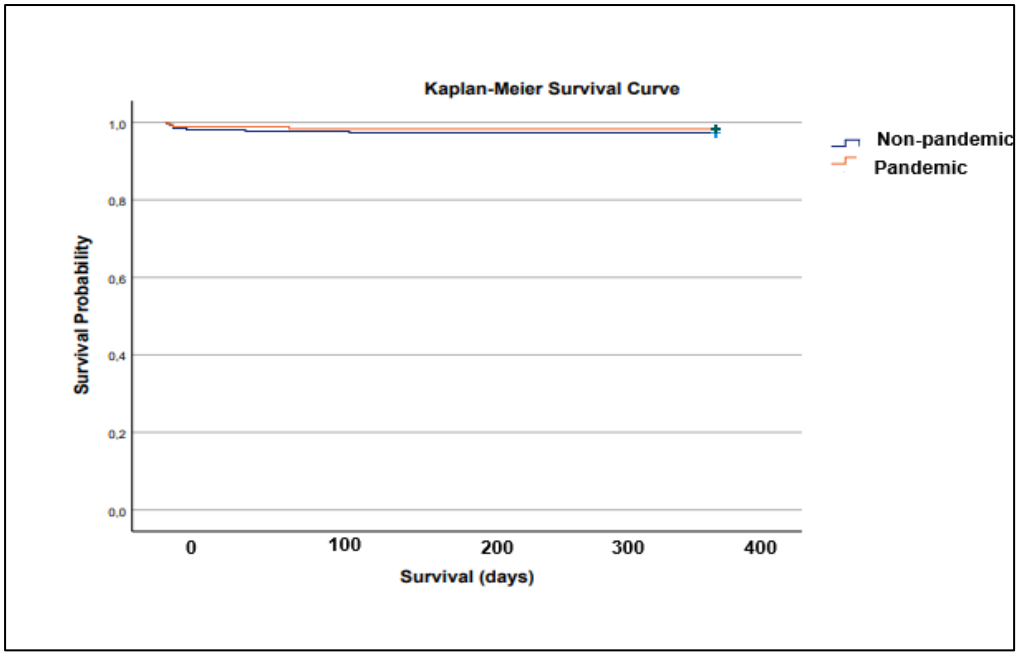

Figure 11: Kaplan-Meier curve for 1-year survival

3.7.3 Perioperative complications

3.7.3.1 MACE

MACE occurred in 21.6% of all patients in the pandemic group and in 20% of patients in the non-pandemic group.

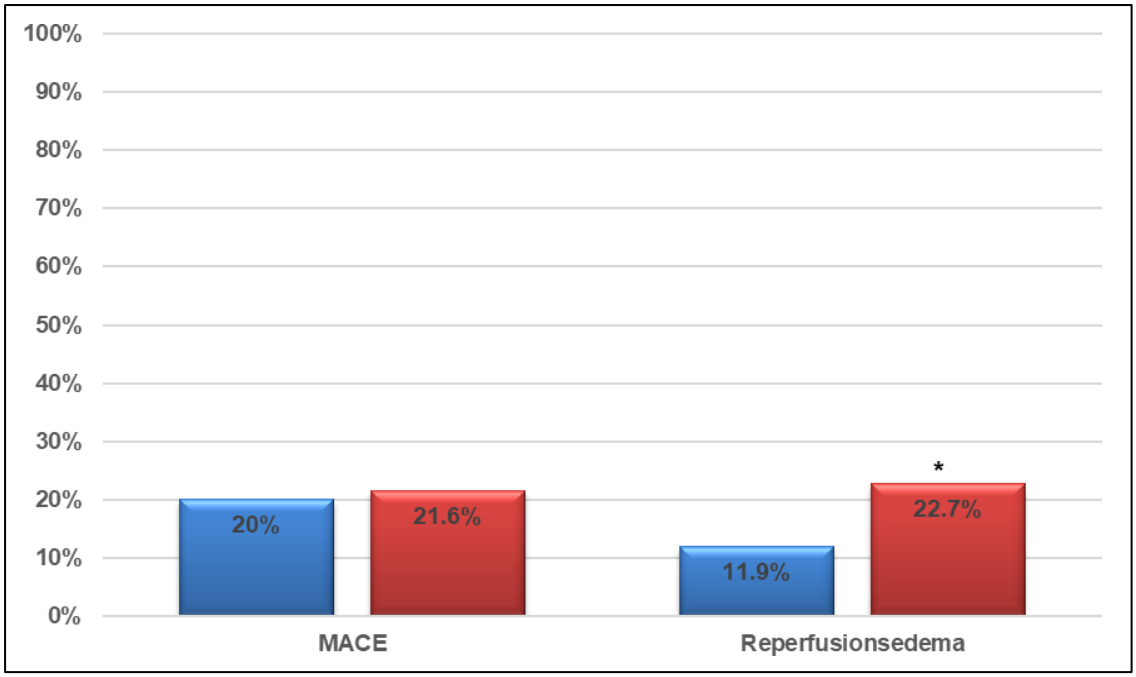

Figure 12: Occurrence of MACE and reperfusions edema in the two groups. *p <0.001. MACE: major adverse cardiac events

3.7.3.2 Reperfusions oedema

A total of 22.7% of patients in the pandemic group developed reperfusion oedema vs. only 11.9% in the non-pandemic group (p = 0.001).

Univariate and multivariate logistic regression analysis showed a significant association between the pandemic group and occurrence of reperfusion oedema (OR 0.460, 95% CI: 0.275-0.770, p = 0.003). However, there was no significant association between waiting time and occurrence of reperfusion oedema (Table 14).

Variates	OR	95% CI for OR		p-value
		Lower	Upper	
Time interval between indication for PEA and PEA	0.997	0.971	1.024	0.843
Time interval between diagnosis and indication for PEA	1.002	0.999	1.006	0.194
Time interval between diagnosis and PEA	1.002	0.999	1.006	0.211
Pandemic	**0.460**	**0.275**	**0.770**	**0.003**

Table 14: Variates included in the multivariate analysis for reperfusions oedema

3.7.3.3 ECMO

A similar percentage of patients (P: 3.4 vs.NP: 3.5%, p = 0.6) needed a veno-arterial ECMO support. Only 1 patient in every study group has needed a veno-venous ECMO support (p = 1.0). Over-all need for ECMO was 3.9% in the P group and 3.9% in the NP group.

4 Discussion

This retrospective study investigated whether a prolonged waiting time due to the COVID-19 pandemic affected pulmonary haemodynamics and outcome of patients with CTEPH undergoing PEA. We can see in the results that there was a 32% decrease in the number of patients that underwent pulmonary endarterectomy (PEA) during the pandemic period compared to the period before the pandemic (P: 260 patients vs. NP: 176 patients). Results also showed that the COVID-19 pandemic led to a prolonged waiting time from diagnosis to pulmonary endarterectomy (PEA) in patients with CTEPH. While there was no influence on waiting time and severity of preoperative pulmonary haemodynamics, occurrence of pulmonary reperfusion oedema as a severe postoperative complication was increased in the pandemic group.
In the following part the clinical extent of our results and possible limitations of the study will be discussed.

4.1 The COVID-19 pandemic

The COVID-19 pandemic was a challenge for health care systems worldwide. According to the Centres for Disease Control and Prevention (CDC), six stages are recognized to every pandemic – investigation, recognition, initiation, acceleration, deceleration and preparation stage. The duration of every stage varies depending on the virus' contagiousness and the reflexes of the public health system. (3)

Due to the well-organised and fast-acting German health care system, the duration of the first three stages was significantly reduced and hospitals were already prepared by the time the acceleration phase had begun. It was accomplished by the rapid mobilisation of the public health infrastructure and an early development of a National Strategy Plan against the pandemic. (79) The Robert-Koch-Institute (RKI), Germany's national health institute, started issuing guidelines for the detection and contamination management by January 16th. Further, at the end of January daily reports regarding the spread of the virus were introduced. Measures to limit the contamination such as physical distancing, travel restriction to and from countries with a high daily infections rate, protection of the older population were initiated.

Regarding the treatment of the COVID-19 patients, a national intensive care register, including ICU capacities and number of COVID-19 patients being treated in total on the ICUs, was established in March 2020.

By increasing the intensive care capacities, at least for a while, german hospitals were able to treat the demanding COVID-19 patients while maintaining a relatively undisturbed care of their usual patient population. (53)

However, the explosive outbreak of the disease and its four waves during the pandemic period (Fig.13), had a significant impact on health care facilities, that also suffered from outbreaks of the virus within the institutes. This led to contamination and further limitation of the already understaffed health care personnel. (72) Thus, the German government was forced to call out long-lasting hard lockdowns and restrict or completely postpone routine surgeries in order to facilitate the treatment of acute life-threatened COVID-19 patients.

During the pandemic waves, although effort was invested into maintaining the essential health services, (82) the limited medical resources led to a delay in treatment of chronic diseases. The consequences of this delay will be witnessed in the post-pandemic period, as it is implied in the literature.

<table>
<tr><th colspan="4">Lockdowns in Germany</th></tr>
<tr><td colspan="2">1st Lockdown:
complete:
13.3.2020-May 2020</td><td colspan="2">2nd Lockdown:
partial:
2.11.2020-14.12.2020
complete:
15.12.2020-Mai.2021</td></tr>
<tr><th colspan="4">COVID-19 pandemic waves in Germany</th></tr>
<tr><td>1st wave:
March-July 2020</td><td>2nd wave:
September 2020-
February 2021)</td><td>3rd wave:
March 2021-July
2021</td><td>4th wave:
August 2021-
January 2022</td></tr>
</table>

Figure 13: COVID-19 pandemic waves and respective lockdowns in Germany. Data from Robert-Koch-Institute database and German Federal Ministry of Health. Although the term lockdown is all-over present, it lacks a universal definition. (28, 56) In Germany, a partial lockdown included restrictions in social gatherings, shutting down of restaurants, theatres, bars, pools, cinemas and gyms and cancelling of social events and limitations in traveling, where during a complete lockdown government facilities, banks, child day care centres and schools and were shut down and routine surgeries were restricted or postponed. (81)

Several studies have investigated the impact of the COVID-19 pandemic on prevention, diagnosis, treatment and outcome in different patient groups. For colorectal surgery in Europe and the United States, the literature shows an influence on preventive examinations by the pandemic.

Studies report an up to 70% decrease in coloscopies in Great Britain and a 25-75% reduction in the USA during the pandemic, leading to a 63% decrease of patients referred to specialized colorectal cancer centres with a suspicion of colorectal cancer. (50) Subsequently, a reduction in the number of colorectal surgeries was also observed. These results could imply an expected worsening of prognosis and 5-year-survival rate due to delayed diagnosis and treatment. (50)

Regarding cardiovascular surgeries, a retrospective observational study conducted in Germany by Böning et al. showed a 29% decrease of intensive care capacities and a 16% decrease of operating room capacities available for cardiac surgery during the lockdowns. 50% of the physicians and 75% of the nursing staff was delegated to the treatment of COVID-19 patients. Around 58% of German heart centres had to reject the treatment of emergency patients during the investigated time interval (from January 1st 2020 to April 30th 2021). (9) Another study by König et al. showed a 15% decrease in cardiac surgeries in Germany from March to September 2020. (66)

Regarding the pulmonary hypertension field, a study conducted in Poland showed a 25-30% decrease in the diagnosis of PH during the COVID-19 pandemic compared to 2019. In the same study, the referral and treatment of the newly-diagnosed PH patients in PH/CTEPH specific centres was 14.7% during the pandemic period and 21.6% in the respective period before the pandemic. (52) However, there has not been a study investigating the impact of COVID-19 pandemic on waiting time and severity of CTEPH in patients undergoing PEA surgery.

4.2 Primary endpoints

4.2.1 Time intervals

In this study we investigated several different time intervals from onset of symptoms until day of PEA surgery. These intervals can be divided into two subgroups based on the course of the disease, the diagnostic algorithm and respective therapy. The first waiting time includes the time interval from onset of symptoms to diagnosis, which is a remarkably long phase in both study groups (62.5 (IQR 40.0-125.75) weeks in the pandemic vs. 61.0 (IQR 26.0-143.0) weeks in the non-pandemic group (p = 0.216). These results could be explained by the slow disease's progression as well as the perplexity of the CTEPH diagnostic algorithm. There are no specific symptoms for CTEPH which makes the diagnosis of the disease rather difficult.

It nevertheless seems that the pandemic did not significantly affect the length of out-of-hospital diagnostic procedures; i.e. family doctor, pulmonologist and reference to a pulmonary hypertension centre took approximately the same time in both study periods.

One possible bias that needs to be considered is that patients operated during the early pandemic period had already been diagnosed and were planned for surgery at the pre-pandemic time. Thus, waiting time in these patients was possibly not affected by the COVID-19 pandemic.

The second waiting time includes the interval between diagnosis, declaration of operability and PEA surgery. In contrast to the first period, it displays a significantly longer time interval in the pandemic group vs. during the pre-pandemic time. Thus, results from this study indicate a prolonged time once patients were admitted to the referred CTEPH centre during the COVID-19 pandemic. These results are in line with the above-mentioned findings on cardiac surgery due to limited capacities. Similar to cardiac surgery, patients after PEA always require postoperative treatment on the ICU. However, especially ICU capacities were strictly limited and primarily reserved for COVID-19 patients during the pandemic. The impact of the COVID-19 pandemic on the treatment of CTEPH patients was possibly even further exacerbated by the small number of specialized centres treating the respective disease worldwide. Our study centre, the Kerckhoff Clinic, is not only the largest PEA centre in Germany but also the only unit fulfilling the criteria for an expert/comprehensive CTEPH centre. (36, 43) Thus, patients from all over Germany and very often from abroad are referred to the Kerckhoff Clinic for the final steps of diagnosis and then PEA surgery. Lastly, as described in the introduction part, PEA patients might also require postoperative ECMO-therapy during the early postoperative period.

However, during the COVID-19 pandemic ECMO-therapy was restrained for COVID-19 patients with a severe disease progression. (71) In summary, limitation of in-hospital capacities and prioritization of COVID-19 patients, especially regarding ICU and ECMO treatment, could explain the results on longer waiting time intervals during the pandemic in our study.

4.2.2 Pulmonary haemodynamic

Evaluating the results regarding the changes in pulmonary haemodynamics, we notice that although PVR and mPAP values significantly increased from time of diagnosis until time of surgery, this change did not differ significantly when pandemic and non-pandemic group are compared to each other.

Interestingly, the time interval between the two measurements – between the RHC examination at the time of diagnosis and the PAC measurements at the day of surgery – is significantly longer in the pandemic group. Thus, while we detected longer time intervals between the two examinations there was no significant difference in change of pulmonary haemodynamics between the study groups. These results might be explained by the slow disease progression along with a delayed diagnosis.

Studies show that the time from onset of the disease until diagnosis can take from 2 to over 5 years and this period plays the cardinal role in the change of the pulmonary haemodynamics. As in the majority of CTEPH patients an incident of PE was observed, Yang et al. conducted a prospective study following patients after PE for up to 10 years. This study shows that the diagnosis of CTEPH after PE takes place within two years after the initial event. (83) These results suggest that the pulmonary haemodynamic changes required to lead to CTEPH diagnosis take around 2 years in patients with a history of PE.

When taking a closer look at the time intervals between the two haemodynamic examinations, we detected a median time of 12 weeks in the non-pandemic group and a median time of 21 weeks in the pandemic group. Referring to the slow disease progression, it can be assumed that during a mean period of 4 to 6 months no significant worsening of the pulmonary haemodynamic is to be expected. This might explain, why the almost doubled waiting time between diagnosis to surgery in the pandemic group had no influence on the severity of pulmonary haemodynamics.

The assumption can be underlined by the pathophysiology of CTEPH and parameters affecting the pulmonary haemodynamics. A review article by Sakao et al. on angio-obliterative PH suggested that the greatest increase in mPAP takes place during the early symptomatic stages of the disease.

Further, by the onset of symptoms and following disease progression, the change in pulmonary artery pressure follows a plateau-like curve. The factors determining the increase during the early disease stages seem to be the pulmonary vascular tone and also the remodelling of the pulmonary vascular bed which is in turn accountable for the severe PH at the late stages of the disease. (63, 70) Sakao et al. also suggested that the pulmonary vascular tone remains a strong determinant of a high pulmonary arterial pressure at the late stages of PH.

Another interesting point from the same study is that the PVR, on the contrary to the mPAP, increases in a time-dependent manner with the disease progression along with the increase from stages 1 and 2 (according to the Heath and Edwards pathological grading method) to higher grades of remodelling (stage 3 and 4) (see Table 15). Referring to these results, a higher increase in mean PVR could be expected in the pandemic group, considering the time interval between the RHC examinations was significantly longer. However, while we did see an increase in mean PVR during waiting time in both groups, it was not significantly higher in the pandemic group. Again, the timepoints of measurements in the study were only 12 and 21 weeks apart, respectively; a time interval relatively short when compared with the long period of up to 5 years referring to disease progression. Unfortunately, there is no data available in the literature that describes the mean length of time for the pathological changes – as described in table 16 – to take place as well as their association with the clinical status of the CTEPH patients.

Potentially reversible
1. Medial thickness of the muscular pulmonary arteries and muscularization of the pulmonary arterioles without intimal alterations.
2. Together with the medial hypertrophy, intimal thickness with cell proliferation in the smaller muscular pulmonary arteries.
3. Intimal obstruction with concentric or eccentric masses of less cellular fibrous tissue in the arterioles and small muscular arteries. Large elastic arteries show atherosclerosis.
Usually irreversible
4. Progressive dilatation of the small arteries with plexiform lesions and muscle hypertrophy is less apparent
5. Chronic dilatation of the small arteries with plexiform and angiomatoid lesions.
6. Necrotizing arteriitis with thrombosis.

Table 15: The Health and Edwards pathological grading method (modified by Heath et al. (31, 63))

Another serious determinant affecting the pulmonary haemodynamics is right heart failure (RHF) that leads to a decrease in cardiac output. The decrease in cardiac output results in an apparent decrease in the pulmonary arterial pressure while the pulmonary vascular disease is still progressing. (63)

A decreased cardiac output at the time of PEA surgery could explain the results regarding mPAP in the present study. No further increase in mPAP was observed possibly due to a severely progressed disease and RHF. Results on heart failure in our study underline this assumption. In the present study 2.8% of the patients in the pandemic group had heart failure with reduced ejection fraction (HFrEF) at the time of surgery compared to only 0.4% in the non-pandemic group. This implies a further progress of the disease that might have impacted the mPAP in these respective patients. Referring to the influence of Cardiac Output on mPAP measurements, it needs to be mentioned that general anaesthesia also commonly leads to a decreased CO. The haemodynamic measurements at the time of surgery were performed under general anaesthesia compared to awake patients for the first RHC examination. This possible bias will be discussed in the limitations part.

Lastly, medical therapy can affect the disease progression and pulmonary haemodynamics in patients undergoing PEA surgery. Since 2015 the sGC-stimulator Riociguat has been used to improve pulmonary haemodynamics in patients with inoperable CTEPH or persisting PH after PEA, improving both pulmonary arterial pressure and PVR in these patients. (74) The medication is also more often used as off-label in patients with severe CTEPH before undergoing PEA surgery. In our study population, 20% of the patients in the non-pandemic and 27% in the pandemic group received the sGC-stimulator as a PH-target therapy. However, there was no association between Riociguat treatment and pulmonary haemodynamics in our study.

4.3 Secondary endpoints

4.3.1 Mortality

The 30-day and the 1-year mortality were not affected by the prolonged waiting time during the pandemic. There was no significant difference in mortality between both study groups. The careful selection of patients and the fact that the study was conducted in a high-volume PEA centre (> 150 operations yearly) are assumingly factors that affected the overall outcome in our study. Studies have shown that the surgical team's and the centre's experience are significant determines of outcome after PEA surgery, (39) with in-hospital mortality in high-volume centres expected to be 2.1% vs. 5.2% in low-volume centres. (8) Overall, 1-year mortality in our study was only 2.3% % with 1.7% in the pandemic and 2.7% in the non-pandemic group. The overall 30-day mortality was 1.4%, 1.1% in the pandemic and 1.5% in the non-pandemic group.

The low number of events could explain why no statistically significant differences were detected between both study groups. As mortality was only a secondary endpoint, the study sample size was not powered for this outcome parameter. A larger study cohort size is probably needed to show an effect on waiting time and mortality in patients undergoing PEA in a specialized centre.

4.3.2 ICU stay

There was no difference observed in the length of ICU stay between both groups. Moreover an even slightly longer ICU stay was shown in the non-pandemic group, which could be explained by the limited ICU capacities during the COVID-19 pandemic. Presumably, patients that did not have severe postoperative complications were released earlier from the ICU in the pandemic group to free-up capacities for other patients. Postoperative admission and treatment on the ICU are highly standardized for CTEPH patients in the respective study centre. All patients remain intubated overnight with slow stepwise de-escalation of mechanical ventilation and extubating after haemodynamic and respiratory stability is achieved and postoperative bleeding is excluded. Given the high surgical experience, the postoperative complication rate is low and most of the patients are allowed to be extubated within 12 hours after the surgery. Further, the nursing personal on the thoracic surgical ward is highly experienced in management of PEA patients regarding respiratory therapy, mobilisation and physiotherapy during the early postoperative phase. Therefore, stable PEA patients can usually be transferred to the normal ward on day 1 or 2 postoperatively.

Re-admission to the ICU is mainly necessary in patients with severe respiratory failure requiring a (non-)invasive respiratory support. The high level of qualification of the staff on the normal ward possibly enabled early transfers from the ICU during the COVID pandemic to ensure respiratory support and intensive care treatment for COVID-19 patients.

4.3.3 MACE

The major adverse cardiac events that were included in the analysis were cardiovascular death, stroke, non-fatal myocardial infarction, new arrhythmia and new congestive heart failure. In our study group, the majority of the reported MACEs were new but non-fatal arrhythmias, while myocardial infarct and stroke were observed by 1 and 2 patients respectively. We did not detect a difference in the occurrence of MACE between both study groups and no influence of waiting time on this secondary outcome. Similar to mortality, with a low number of events of MACE the study population was possibly too small to detect any statistical difference. In the literature, there is poor evidence regarding MACE after PEA. Comparable to our results, occurrence of MACE after PEA is also low in the literature. (64)

4.3.4 Reperfusion oedema

A possible severe and specific postoperative complication after PEA is a pulmonary reperfusion oedema (RPE). It is a high-permeability oedema that appears in the lung areas that were previously occluded and reperfused after the surgical removal of the thrombotic material. RPE occurs usually within 48 hours after PEA surgery but can also present itself in a later postoperative period. Its incidence varies widely from 9.6 to 20.3%, (55) and in some studies, depending on the centre and definition, an incidence of up to 50% has been reported (2, 38). The definition used in the study centre is in accordance with Jenkins et al. and based on a Horovitz index <300mmHg, radiographic opacity in reperfused lung areas and exclusion of other causes for these clinical signs. (40) Studies indicate that increased perfusion of the formerly occluded pulmonary vessels, inflammation, perioperative ischemia and ventilator-associated lung injury are responsible for RPE. Its severity varies from mild, which can be treated with high-flow oxygen and non-invasive respiratory therapy to severe respiratory failure and alveolar haemorrhage treated with invasive respiratory therapy, prone position and ECMO. (49)

The overall occurrence of reperfusion oedema in the study population was 16.3%, with the complication occurring significantly more often in the pandemic group (23% vs 12%), OR 0.46, p=0.003). An independent association between pandemic and reperfusion oedema was shown in our study (OR 0.46, p = 0.003). While the change in mPAP in both groups both from baseline to surgery and from preoperative to postoperative values was not significantly different in the two groups, the severity of preoperative mPAP value had an association with occurrence of RPE in our study group. Further studies are needed to analyse whether mPAP is an independent risk factor for RPE in patients after PEA surgery.

4.3.5 ECMO support

Both VA- and VV- ECMO, as a bridging therapy after PEA have already been reported in literature since 2005. (1) VA-ECMO is selected in patients with decompensated right heart failure secondary to residual PH and difficulty in weaning from CPB, while VV-ECMO is mainly preferred by refractory reperfusion oedema and massive endobronchial bleeding. (12) The need for ECMO support after PEA is reported to be around 4.7% with a survival rate of over 50%. (12) That correlates with the results in our study where around 3.8% of patients in both study groups required an ECMO bridging therapy after PEA. Most of the patients required a VA-ECMO indicating that the main cause for ECMO therapy was rather the short-term usage in cases of severe endobronchial haemorrhage than severe reperfusion oedema in need of VV-ECMO. (26) However, there was no difference in both groups, probably because the study population was too small to show a significant difference. The results are however in accordance with literature about ECMO therapy after PEA.

4.4 Study limitations

4.4.1 Study design

The study was a single-centre retrospective cohort study hence bearing the limitations of every retrospective study, i.e. missing data, inferior level of evidence, selection and recall biases. As a single-centre study, conducted in a high-volume PEA centre, its results may not represent the reality in all other centres and are therefore not fully externally applicable, especially considering lower-volume centres with higher mortality. Nevertheless, outcomes (like mortality and reperfusion oedema) and patient characteristics correspond with current literature and therefore can be regarded as representative.

We did not detect any difference in secondary outcome parameters between both groups. The sample size in our study might have been too small to detect statistical differences for endpoints like short- and long-term mortality.

Another significant parameter regarding the postoperative outcome after PEA that was not analysed in the study was the occurrence of residual pulmonary hypertension. Residual pulmonary hypertension is a specific postoperative parameter after PEA that affects the quality of life and long-term mortality (34) and occurs up to 50% after PEA. To set the diagnosis of residual PH, a postoperative mPAP≥30mmHg must be measured. However, the measurements taken directly postoperative do not seem to correlate with residual PH. The measurement has to take place at least 3 months up to 1 year after PEA to ensure the diagnosis of residual PH. (2) The retrospective design of the study did not allow us to get access to this follow-up information, that usually takes place in the referral PH centre.

Due to the retrospective design of the study, we were unable to gather data regarding the change in quality of life between the two groups during waiting time. Results of our study show that 36% of the patients in the pandemic group vs. 24% in the non-pandemic group needed a long-time oxygen therapy by their admission to hospital for the surgery. LTOT is a factor negatively affecting the quality of life of patients along with heart failure, which was also significantly more common in the pandemic group. Especially LTOT restricts daily life in CTEPH patients and this negatively effects quality of life. (29, 62, 84) In line with this, various studies from the cardiac surgery literature show a correlation between waiting time to surgery and patient satisfaction. (4, 7, 65) The same dissatisfaction could also be present in the PEA patients, especially considering an already long time from onset of symptoms until diagnosis due to the slow progression of disease and the difficulties in diagnosis. Prospective studies on patient-centred outcomes regarding quality of life are therefore needed in this patient population.

4.4.2 Haemodynamic measurements

An important point that needs to be considered when the results are being analysed is the condition under which the RHC measurements took place. The initial RHC examination at the time of diagnosis was performed in awake patients. In contrast, the measurements at the day of surgery were conducted after induction of anaesthesia. It is known that general anaesthesia has an impact on cardiac output, which in turn affects the pulmonary haemodynamics. Therefore, we cannot rule out an influence on general anaesthesia on haemodynamic values in our study. However, a direct impact of anaesthetics on mPAP and PVR has not been proven, except for ketamine that seems to raise the pulmonary artery pressure. (32) Ketamine was not routinely used for the induction of anaesthesia in our study population; therefore, we assume that the anaesthetic agents used for induction and maintenance of anaesthesia in our patients did not affect pulmonary measurements.

Next to the employed anaesthetic regimen, another influencing factor in patients under general anaesthesia is mechanical ventilation. Studies indicate that it affects the right ventricle ejection flow (RVEF). (30) Positive end-expiratory pressure has also been shown to decrease CO which in turn could lead to elevated PVR measures. (14) An influence of mechanical ventilation on our data cannot be ruled out and must be seen as a limitation on our results regarding comparison between the measurements within each study group. However, both the influence of general anaesthesia as well as mechanical ventilation as possibly limitations apply to both study groups equally; hence, a comparison between pandemic and non-pandemic group regarding pulmonary haemodynamics should not be affected.

Owning to retrospective study design, measurements were not performed under the same conditions regarding normal arterial blood pressure, normocarbia and normoxaemia. The systematic blood pressure for example affects the right ventricular filling and perfusion and sequentially the pulmonary haemodynamics. (57) Hypoxaemia and hypercarbia lead to elevated PVR values. (58)

Lastly, we did not evaluate the respective obstruction ratio for both patient groups. According to Jujo et al., (42) PVR and mPAP correlate positively with the obstruction ratio of the pulmonary artery. The obstruction ratio is the ratio of the luminal and medial area to the vascular area of the pulmonary muscular arteries and was shown by Jujo et al. to play a role in the pulmonary haemodynamics in patients with CTEPH. This ratio was not included in the present study; therefore, it is not known whether the degree of pulmonary arteriopathy, expressed by the obstruction ratio, was affected by a prolonged waiting time during the COVID-19 pandemic. These possible limitations need to be considered when interpreting results from our study.

4.5 Perspective

This study is the first to investigate the influence of waiting time on pulmonary haemodynamics in CTEPH patients undergoing PEA surgery. The COVID-19 pandemic provided the ”opportunity“ to evaluate disease progression and pulmonary haemodynamics with time and a possible impact of waiting time on outcome after PEA surgery. Results from our study show a significantly longer waiting time in patients during the COVID-19 pandemic but without any differences in pulmonary haemodynamics or outcome compared to the pre-pandemic period. It showed that there is certainly a need for larger, multi-centre, prospective studies, that will try to detect factors affecting the pulmonary haemodynamics but also look at quality of life in these patients. Focus should also be placed on the influence of medical therapy as part of the multi-modal therapy of CTEPH patients. What should also be further investigated are the factors contributing to residual pulmonary hypertension. Of equal importance and necessity are studies examining the pathological evolvement of the disease over the time of disease progression. Our study did show a significant increase in waiting time during a pandemic; hence, the planning and triage of treatment of CTEPH patients in high-volume centres should be optimized.

5 Abstract

Background: The COVID-19 pandemic challenged health care systems worldwide with its high mortality rate but also by limiting intensive care unit capacities leading to a critical delay in elective surgeries. Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare and underdiagnosed disease often resulting in a delayed treatment. Life expectancy of patients with CTEPH is only 1 to 3 years when left untreated. Pulmonary endarterectomy (PEA) is the only curative treatment approach. (76) During the COVID-19 pandemic PEA cases were postponed leading to an increased waiting time. The impact of a prolonged waiting time on preoperative pulmonary haemodynamics and outcome of patients after PEA has not been investigated.

Methods: We conducted a retrospective single-center study at the Kerckhoff Clinic, Bad Nauheim. All patients with confirmed CTEPH diagnosis, that underwent a PEA surgery from March 1st 2018 till December 31st 2021 were included in the study and were divided in two groups: pandemic (P) and non-pandemic (NP). The main exposure variable was waiting time from onset of symptoms until PEA surgery. The primary endpoint was preoperative mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR). Secondary endpoints included 30-day and 1-year mortality, length of ICU stay and prevalence of postoperative MACE and reperfusion pulmonary oedema (RPE).

Results: A total of 436 patients were included into analysis (P: n=176; NP: n=260). Though mean waiting time from CTEPH diagnosis until PEA surgery was significantly longer in the pandemic group (P: 60±104 weeks vs. NP: 22±32 weeks, p<0.001), there was no difference in preoperative mPAP and PVR values between both groups. Waiting time was not associated with increased preoperative pulmonary haemodynamics. Short- (30-day-mortality P: 1.1% vs. NP: 1.5%, p = 0.721) and long-term outcome (1-year mortality P: 1.7% vs. NP 2.7%, p = 0.5) did not differ between both groups. There was no association between waiting time and occurrence of MACE or the length of ICU stay. An increased risk for development of RPE (OR 0.433, 95% CI: 0.226-0.827, p = 0.011) was detected.

Conclusion: The COVID-19 pandemic led to an increased waiting time for PEA surgery in patients with CTEPH. While we did not show an impact on preoperative pulmonary haemodynamics, an increased risk for RPE – a severe complication after PEA surgery – was detected in our study cohort.

6 Zusammenfassung

Hintergrund: Die COVID-19 Pandemie einhergehend mit einer hohen Mortalität und der Einschränkung von Intensivkapazitäten führte zu einer deutlichen Verzögerung elektiver Operationen und stellte eine Herausforderung für die weltweiten Gesundheitssysteme dar. Chronisch thromboembolisch pulmonale Hypertonie (CTEPH) ist eine seltene und unterdiagnostizierte Krankheit. Die Pulmonale Endarteriektomie (PEA) ist die einzige kurative Therapieoption. (76) PEA-Operationen wurden jedoch, während der COVID-19 Pandemie verschoben, was zu längeren Wartezeiten führte. Der Einfluss dieser Wartezeit auf die präoperative pulmonale Hämodynamik und das Outcome nach PEA wurde bisher nicht untersucht.

Methodik: Es wurde eine retrospektive, single-center Studie an der Kerckhoff Klinik in Bad Nauheim, Deutschland durchgeführt. Eingeschlossen wurden alle erwachsenen Patienten mit bestätigter CTEPH Diagnose, die sich eine PEA im Zeitraum vom 1.3.2018 bis zum 31.12.2021 unterzogen haben. Die Patienten wurden in zwei Gruppen eingeteilt: Pandemie (P) und Nicht-Pandemie (NP). Die Hauptexpositions-variable war die Wartezeit vom Symptombeginn bis zur PEA-Operation. Als primäre Endpunkte wurden der mittlere pulmonal arterielle Druck (mPAP) und der pulmonale Gefäßwiderstand (PVR) festgelegt. Die sekundären Endpunkte waren 30-Tage und 1-Jahres Mortalität, Dauer des Aufenthalts auf der Intensivstation (ITS) sowie Auftritt von Major adverse cardiac events (MACE) und das Reperfusionsödem (RPE).

Ergebnisse: Es wurden insgesamt 436 Patienten analysiert (P: n=176, NP: n=260). Trotz der signifikant länger mittlerer Wartezeit von CTEPH Diagnose bis zur PEA in der Pandemie Gruppe (P: 60±104 Wochen vs. NP: 22±32 Wochen, $p < 0.001$), wurde kein Unterschied in den präoperativen mPAP und PVR-Werten zwischen den Gruppen festgestellt. Die Wartezeit war nicht mit einer Verschlechterung der pulmonalen Hämodynamik assoziiert. Kurz-(P:1.1% vs. NP:1.5%, p=0.721) und Langzeitüberleben (P:1.7% vs. NP:2.7%, p=0.5) haben sich nicht signifikant zwischen den Gruppen unterschieden. Es wurde keine Assoziation zwischen Wartezeit und Auftritt von MACE oder Dauer des Aufenthalts auf der ITS festgestellt. Ein erhöhtes Risiko für RPE während der Pandemie (OR:0.433, 95% CI: 0.226-0.827, p=0.011) konnte gezeigt werden.

Fazit: Die COVID-19 Pandemie hat zu einer Verlängerung der präoperativen Wartezeit bei CTEPH Patienten geführt. Obwohl kein Einfluss der Wartezeit auf die präoperative pulmonale Hämodynamik nachgewiesen wurde konnte, zeigte sich ein erhöhtes Risiko für RPE während der COVID-19 Pandemie.

7 List of abbreviations

ACT	Activated clotting time
BMI	Body mass index
BPA	Balloon pulmonary angioplasty
CO	Cardiac output
COVID19	Corona Virus Disease 19
CPB	Cardiopulmonary Bypass
CTE(P)D	Chronic thromboembolic (pulmonary) disease
CTEPH	Chronic thromboembolic pulmonary hypertension
DHCA	Deep hypothermic cardiac arrest
DOACs	Direct oral anticoagulants
dPAP	Diastolic pulmonary artery pressure
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise testing
CT	Computed tomography
CTPA	Computed tomography pulmonary angiography
DVT	Deep venous thrombosis
dPAP	Diastolic pulmonary artery pressure
DSA	Digital subtraction angiography
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
ERS	European respiratory society
ESC	European society of cardiology
ET	Endothelin
FC	Functional class
FDA	Food and drug administration

Fig.	Figure
HFrEF	Heart failure with reduced ejection fraction
I	Current
ICU	Intensive care unit
LAP	Left atrial pressure
LTOT	Long-time oxygen therapy
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac events
MD-CT	Multidetector computed tomography
MDT	Multidisciplinary team
mPAP	Mean pulmonary artery pressure
MRI	Magnetic resonance imaging
NIBP	Non-invasive blood pressure
NO	Nitric oxide
PA	Pulmonary artery
PAC	Pulmonary artery catheter
PCWP	Pulmonary capillary wedge pressure
P(A)E	Pulmonary (artery) embolism
PEA	Pulmonary endarterectomy
PGI_2	Prostacyclin
P(A)H	Pulmonary (arterial) haemochromatosis
PEEP	Positive end-expiratory pressure
Preop.	Preoperative
Postop.	Postoperative
PVOD/PCH	Pulmonary veno-occlusive disease/pulmonary capillary hypertension
PVR	Pulmonary vascular resistance
Qp	Pulmonary flow

R	Resistance
RHC	Right heart catheter
RHF	Right heart failure
ROC	Receiver operating characteristic
RVEF	Right ventricular ejection flow
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SD	Standard deviation
sGC-cGMP	Soluble Guanylate Cyclase-cyclic Guanosine Monophosphate
SVR	Systemic vascular resistance
sPAP	Systolic pulmonary artery pressure
STROBE	Strengthening the reporting of observational studies in epidemiology
Tab.	Table
TAPSE	Tricuspid annular plane systolic excursion
TTE	Transthoracic echocardiography
UCSD	University of California San Diego
USA	United States of America
V	Voltage
VA	Ventriculoatrial
VA-ECMO	Veno-arterial extracorporeal membrane oxygenation
V/Q	Ventilation/perfusion
Vs	Versus
VV-ECMO	Veno-venous extracorporeal membrane oxygenation
WHO	World health organisation

8 Table directory

Table 1: Risk factors associated with CTEPH 2

Table 2: Updated classification of PH 3

Table 3: WHO functional classification 4

Table 4: Clinical symptoms of CTEPH 6

Table 5: Typical characteristics in CTPA indicating CTEPH 10

Table 6: Inclusion criteria 24

Table 7: Exclusion criteria 24

Table 8: Software programs used for collection and statistical analysis of the data 30

Table 9: Choice of co-variables 31

Table 10: All patient characteristics as well as CTEPH and surgical characteristics for the study cohort 34

Table 11: Pulmonary hemodynamic in the two study groups 37

Table 12: Results of regression analysis of diverse time intervals and difference in mPAP from time of diagnosis to time of operation 39

Table 13: Results of regression analysis of diverse time intervals and difference in PVR values from time of diagnosis to time of operation 39

Table 14: Variates included in the multivariate analysis for reperfusions oedema 42

Table 15: The Health and Edwards pathological grading method 48

9 List of illustrations

Figure 1: CTEPH Diagnostic algorithm modified by ESC/ERS guidelines 2022 8

Figure 2: Therapeutic options based on obstruction localisation 15

Figure 3: Historical landmarks of the evolution of PEA 17

Figure 4: Screening process flow chart 25

Figure 5: Median time interval from onset of symptoms till PEA between the pandemic and non-pandemic group in weeks. PEA pulmonary endarterectomy 35

Figure 6: Median time interval from diagnosis of CTEPH to PEA between pandemic and non-pandemic group in weeks 36

Figure 7: Median time interval from the first measurement in RHC to the measurement before surgery 37

Figure 8: Change in mean PVR (in Wood Units-WU) value in the two groups from time of diagnosis to time of surgery 38

Figure 9: Change in mean mPAP (in mmHg) value in the two groups from time of diagnosis to time of surgery 38

Figure 10: Kaplan-Meier curve for 30-days-survival 40

Figure 11: Kaplan-Meier curve for 1-year survival 40

Figure 12: Occurrence of MACE and reperfusions edema in the two groups 41

Figure 13: COVID-19 pandemic waves and respective lockdowns in Germany 44

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