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Non-invasive Dx of PH in COPD: ECG, Radiological Measures, Echo, Myocardial Scintigraphy & Psychotherapy in Emergency/Pediatric Settings

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Abstract:

Pulmonary hypertension (PH) is a common complication in patients with chronic obstructive pulmonary disease (COPD), contributing significantly to morbidity and mortality. This article explores non-invasive diagnostic methods for detecting PH in COPD patients, including electrocardiography (ECG), radiological measurements, echocardiography, and myocardial scintigraphy. These diagnostic tools are essential in emergency and pediatric settings, where rapid and effective identification of PH is critical. The role of the psychotherapist is also examined, particularly in managing the psychological impact of COPD and PH, as patients often experience significant emotional distress, including anxiety and depression. Psychotherapeutic interventions, such as cognitive-behavioral therapy (CBT), can improve patients' mental well-being, supporting better overall management of the disease. This comprehensive approach, combining physical and psychological treatment, enhances the quality of life for COPD patients and improves their ability to cope with the challenges of living with PH.

Abbreviation Term

PH Pulmonary Hypertension

COPD Chronic Obstructive Pulmonary Disease

ECG Electrocardiogram

CT Computed Tomography

MRI Magnetic Resonance Imaging

PAP Pulmonary Arterial Pressure

RHC Right Heart Catheterization

ECHO Echocardiography

SPECT Single Photon Emission Computed Tomography

PFT Pulmonary Function Test

6MWT 6-Minute Walk Test

NT-proBNP N-terminal Pro B-type Natriuretic Peptide

RV Right Ventricle

LV Left Ventricle

RAC Right Atrial Compliance

MIBI Myocardial Imaging with Technetium-99m (commonly used in myocardial scintigraphy)

ECMO Extracorporeal Membrane Oxygenation

B-type BNP B-type Natriuretic Peptide

1. Introduction

Introduction

Pulmonary hypertension (PH) is a serious complication commonly associated with chronic obstructive pulmonary disease (COPD), leading to significant morbidity and mortality. While traditional diagnostic approaches such as right heart catheterization (RHC) have been considered the gold standard, these methods are invasive, costly, and not easily accessible in all clinical settings. The increasing demand for efficient and non-invasive diagnostic techniques has resulted in significant advancements in the use of electrocardiogram (ECG), radiological measurements (including computed tomography (CT) and magnetic resonance imaging (MRI)), echocardiography (ECHO), and myocardial scintigraphy (SPECT) as diagnostic tools in both emergency and pediatric settings.

In particular, PH in pediatric populations remains underdiagnosed due to the challenges associated with detecting the condition at early stages. The ability to use non-invasive methods for diagnosing PH in these settings can help prevent unnecessary invasive procedures, while also improving the quality of care. In emergency settings, timely diagnosis and accurate monitoring of PH are crucial, as these patients often experience rapid disease progression or exacerbations. Additionally, emerging technologies such as biomarkers and advanced imaging techniques promise to complement traditional diagnostic methods and offer more precise, real-time information on the hemodynamic state of patients with COPD and PH.

The integration of non-invasive techniques for both diagnosis and ongoing management of PH is particularly beneficial for patients with COPD, as these tools provide a means of assessing the severity of PH and monitoring treatment progress with minimal risk. Furthermore, the psychological impact of COPD and PH diagnosis, especially in pediatric patients, requires attention, as mental health disorders can influence patient outcomes. These diagnostic tools, while primarily used for medical management, can also assist healthcare providers in understanding the psychological burden on patients, which is a critical component of comprehensive care.

The role of the psychotherapist in managing pulmonary hypertension (PH) in chronic obstructive pulmonary disease (COPD) patients is crucial, as it addresses the psychological and emotional aspects of the disease. COPD with associated PH often leads to significant emotional distress, such as anxiety and depression, due to the limitations on physical activity, breathlessness, and uncertainty regarding the progression of the disease. A psychotherapist can provide vital support through therapeutic interventions, particularly cognitive-behavioral therapy (CBT), to help patients cope with these emotions and improve their mental resilience. Therapy can focus on reducing anxiety by developing coping strategies, promoting relaxation techniques, and enhancing self-efficacy. Additionally, the psychotherapist plays a critical role in helping patients manage the psychological burden of a chronic illness, thereby improving their quality of life. By addressing both the mental and emotional well-being of COPD patients, psychotherapists contribute to a holistic treatment approach that complements the physical management of PH, ultimately leading to better patient outcomes and satisfaction (Elwing & Panos, 2008; Kovacs et al., 2022; Vizza et al., 2021).

This paper explores the comparison of ECG, CT, MRI, ECHO, and SPECT as non-invasive diagnostic tools for PH in COPD, focusing on their applications in emergency and pediatric settings. It also examines the potential role of these techniques in supporting psychological care for patients, emphasizing the holistic approach to managing PH.

2. Overview of Chronic Obstructive Pulmonary Disease (COPD)

Patients with chronic obstructive pulmonary disease (COPD) frequently have elevated pulmonary arterial pressures. Elevated pulmonary artery pressure is an independent predictor of mortality in patients with COPD (Elwing & J Panos, 2008). Pulmonary hypertension is much more likely to be the direct cause of death or hospitalization than are underlying COPD exacerbations. Pulmonary hypertension was found in 20% of 277 patients with COPD who underwent right heart catheterization (Olschewski, 2021). The prevalence of severe pulmonary hypertension (mean pulmonary artery pressure greater than 35 mmHg) is as high as 10%. However, only 0.5% of the 60 million people worldwide with COPD are suffering from severe pulmonary hypertension (PH) related to COPD. This is in contrast to 50–70% of COPD patients who have echocardiographic evidence of even mild to moderate PH. Several types of measurement of increased systemic inflammation activity and acute lung inflammation seem to be associated with pulmonary hypertension (PH) in this disease. Inflammation of the lung may lead to increases in vascular resistance, hypoxic pulmonary vasoconstriction, vessel wall proliferation, and functional and structural changes in the distal vessels, most fundamentally to the remodeling of arterioles. This process is described in the onset of chronic obstructive pulmonary disease (COPD)-associated PH, contributing to the increase in pulmonary pressure.

COPD is the most common lung disease associated with pulmonary hypertension, with a reported prevalence of 20-90%. Patients with COPD-related pulmonary arterial hypertension often have mild to no symptoms at rest, but an increase in symptoms with activities is characteristic. Exertional dyspnea is the most common symptom, often followed by fatigue, chest pain, or syncope. Signs include the accentuation of the pulmonary component of S2 and a parasternal heave secondary to the pulmonary hypertension. Late signs reflect an increased right ventricular (RV) workload and pulmonary hypertension at rest and include RV heave, hepatomegaly, and ascites. The management of chronic obstructive pulmonary disease-related pulmonary hypertension needs to be individualized to manage the underlying lung disease and the pulmonary arterial hypertension (PH). The treatment of chronic obstructive pulmonary disease is centered on lifestyle and pharmacologic interventions to minimize disease symptoms and improve functional status. Similarly, given the strong association between chronic obstructive pulmonary disease and pulmonary hypertension, the goal of the treatment of chronic obstructive pulmonary disease-related pulmonary hypertension is to improve functional and hemodynamic capacity. (Olsson et al.2023)(DuBrock et al.2021)(Zhang et al.2022)(Kovacs et al.2022)(Arif et al.2022)(Vizza et al.2021)(Dauriat et al.2021)

3. Pathophysiology of Pulmonary Hypertension in COPD

Pulmonary hypertension (PH) is an established complication of chronic obstructive pulmonary disease (COPD) and a well-recognized cause of maternal morbidity and mortality, with most deaths resulting from right ventricle failure. Nevertheless, PH in COPD is underdiagnosed as the recommended criteria for the echocardiographic diagnosis are rarely fulfilled. PH in COPD is generally thought of as a consequence of hypoxia and global vascular occlusion distal to the arterioles leading to passive flow limitation. Still, the current understanding of the pathophysiology, prognosis, and response to treatment of PH in COPD remains limited. This article reviews the latest research on and current understanding of the pathophysiology of PH in COPD, presents an overview of the currently available evidence on the effects of treatments for PH in COPD, and makes suggestions about possible next steps to advance the characterization of this under-researched phenotype (Naeije & A Barberà, 2001).

Pulmonary vessels are compliant low-resistance conduits with the high distensibility of the pulmonary circulation allowing it to accommodate the entire cardiac output with an average pressure drop of 5–10 mmHg. In normal circumstances, a pulmonary pressure similar to that in the aorta can be shown in the first few centimeters of the pulmonary artery, whereas in the setting of established chronic obstructive pulmonary disease (COPD), pressures single that of the preceding segment can still be measured at the lobar level. Moreover, in mechanically ventilated patients with severe airflow limitation, the

distribution of mean pulmonary artery pressure is strikingly flat, peaking in the upper lobes but not differing appreciably between them, or between lower lobes, from the normal (Krompa & Marino, 2022).

4. Importance of Early Diagnosis

Progressive pulmonary hypertension (PH) is often associated with the common presentation of chronic obstructive pulmonary disease (COPD), even when such a combination of progressive PH and COPD symptoms can be traced back through many years. That is, in its early stages, PH produces only nonspecific symptoms such as breathlessness on exertion, light-headedness, malaise or peripheral edema. Because these symptoms are common to many other medical conditions, they are often missed, ignored or attributed to normal aging. This would allow the disease to progress unnoticed for long periods of time and remain untreated. By the time symptoms are severe enough to prompt a referral to a specialist, the PH often is advanced. Given this knowledge gap, the generation and delivery of new tools for early detection, recognition and tracking of progressive COPD-PH disease are required (Olschewski, 2021). Chronic lung diseases are a common and strong risk factor for the development of PH. An epidemiological study demonstrated that COPD patients have a 6.5 times higher risk to develop PH than the general population. Furthermore, in COPD, even mildly elevated pulmonary arterial pressures are associated with an increased mortality risk. An autopsy study estimated the prevalence of PH in patients who died from COPD as 30%. For these reasons, the sixth World Symposium on Pulmonary Hypertension (WSPH) suggests to perform an echocardiography in every patient with chronic lung disease at the time of first diagnosis. The same panel emphasizes complying with a quality-controlled echo procedures and sending the results to specialists in case of elevated pulmonary arterial pressure. It is reasonable the majority of primary care physicians and pulmonologists do not follow these recommendations due to an additional burden of workmanship and incomplete reimbursement for this procedure (L. Hewes et al., 2020). Symptoms of PH are similar to those of many other pulmonary, cardiologic and hematologic conditions. Sometimes, patients are not specific and other times they are unspecific, pointing to more than one reason for further evaluation. Similarly, in its early stages, PH could be detected only during specific tests or measurements is indeed the detection will be missed in general physical examinations. A unique feature found here is that echocardiographic evaluations are rare for most individuals are not involved (the chronically ill and elderly, for example) during routine clinical care. Furthermore, the inclination of many subjects to avoid new tests or treatments to be more realistically reflects the path of the undetected progression of the disease. (Vizza et al.2021)(Arif et al.2022)(Torres-Castro et al.2021)(Parikh et al.2022)

5. Traditional Diagnostic Methods

Chronic obstructive pulmonary disease (COPD) is an umbrella term for a number of respiratory conditions including chronic bronchitis and emphysema. It is characterised by persistent respiratory symptoms and airflow limitation, and it's not fully reversible. The current diagnostic criteria for COPD are based on the presence of a post-bronchodilator forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio lesser than 0.70 (Coste et al., 2019). The severity is graded based on level of airflow limitation as per the Global Initiative for Obstructive Lung Disease (GOLD) classification system, which is based on FEV1 percent predicted. This current grading considers less relevant but important parameters, as the classic GOLD stages are currently based on clinical criteria. Nowadays, are you Grade II or Grade D GOLD? The increased risk of exacerbations in patients with chronic obstructive pulmonary disease (COPD) often necessitates that a peak flow meter be used to monitor their condition. This affordable and proven device can alert patients at an early stage so they can act to reduce the severity of the exacerbation, such as by taking effective medication to relieve symptoms and open up the airways. Are you using a peak flow meter? Pulmonary hypertension (PH), a more dangerous diagnosis, is recognised by the World Health Organization when resting mean pulmonary arterial pressure (mPAP) is equal or higher than 25 mmHg at rest. The prevalence of PH in COPD has been shown to be as high as 70% of all COPD-subjects when diagnosed by right heart catheter. Because of this devastating comorbidity clinicians have to rely on echocardiographic-based incidence or risk-based prediction models that show very variable, often poor results. In addition to the discussion of severe COPD cases referred to above, what is the original scope of the paper you are writing? Just concerning COPD-endotype? or the focus is on a new diagnostic method? PH has a devastating impact on COPD patients; it is associated with increased mortality, hospital stay and mortality mainly through right heart failure. At this date, PH diagnosis is unique, and term definition is based only on right cath measurement. Hence, despite the above-mentioned broad evidence of PH prevalence, COPD-patients are not routinely recommended RHC. On the other hand, information

coming from echocardiographic-based PH assessment is quite unreliable in COPD. Is it because graphic-exhaustive cardiovascular evaluation is expensive? or is it because chronic respiratory disease is under the cardiopulmonary coupling assessment? To complicate the picture further, about 90% of COPD-subjects have a new moderate to very high risk on 2019 GOLD assessment force them to referral to more exhaustive diagnostic procedures. (Zhang et al.2022)(Kovacs et al.2022)(Vizza et al.2021)(Arif et al.2022)(Dauriat et al.2021)

5.1. Right Heart Catheterization

Pulmonary hypertension (PH) is defined as an elevated mean pulmonary artery pressure (>20 mmHg at rest) required by right heart catheterization (RHC) (Metella Refini et al., 2021). The prevalence of PH in chronic obstructive pulmonary disease (COPD) patients is controversial and ranges from 20% to 90% depending on the population studied and methodological issues. PH in COPD is usually associated with hypoxemia, with variable degrees of hypercapnia, and is most severe in advanced stages of COPD. The diagnosis is important because it is a predictor of greater oxygen consumption during exercise and has a significant impact on survival and body mass index airflow obstruction and dyspnea index. Currently, RHC is considered the gold standard examination for diagnosing PH, although a combination of noninvasive echocardiographic approaches would be a more desirable and lower-risk alternative than RHC. The current recommended echocardiographic scheme for the DETECTION of PH includes assessment of the estimated right ventricular systolic pressure (eRVSP) and the morphological and etiological evaluation of the right atrium and ventricle. However, there are further, extremely valuable echocardiographic parameters that could complement this and provide a more comprehensive, multifaceted view of the RV, for example, the RV regional wall motion, and RV 2D STE imaging. (Zhang et al.2022)(Vizza et al.2021)(Kovacs et al.2022)(Arif et al.2022)

5.2. Echocardiography

After chronic thromboembolic pulmonary hypertension, pulmonary hypertension (PH) is most commonly seen in patients with COPD. Echocardiographic examination is employed for the evaluation of these patients for PH. Echo-doppler assessment of the patients with chronic obstructive pulmonary disease (COPD) may demonstrate pulmonary hypertension as well as diseases of the left heart. This work aimed to investigate the ability of echocardiographic variables of the left heart to predict the presence of echocardiography-detected PH in patients with COPD (Buklioska-Ilievska et al., 2019). Demographic data, blood biochemistry, pulmonary function tests (PFT), and echo-doppler examinations of the patients were reviewed from files, retrospectively. Correlation analyses were done and variables with significant correlations or variables known to be related to COPD and PH were selected for logistic regression analysis. Of the 61 patients, 30 were having echocardiographic evidence of PH and 31 patients were having no PH. For obtaining a good view, 16 of the patients were excluded. When the area under the curve (AUC) was studied, the following findings were determined as significant predictors of PH in COPD patients: left atrial end-systolic volume (LAVmax), cardiothoracic index (CT index) and E/E'septal ratio. It was concluded that the selected markers should be kept in mind in patients with COPD, especially those who were likely to be consulted. The present research found that the LAVmax, CT index, and E/E'septal ratio were correlated to other echo-doppler variables and known to be related to COPD and PH. However, there was no previous literature demonstrating that these parameters could predict PH in patients with COPD. It is known that the left heart diseases and chronic lung disease may co-exist. According to these, pulmonary venous hypertension may develop as a result of left heart diseases and systolic and diastolic left ventricular dysfunction may also be seen in patients with COPD. PH in the setting of COPD has been accepted as group C of PH and it is generally defined as mPAP $\geq$ 20 mmHg. PH may develop in any stage of COPD but in the terminal stage, the prevalence of PH increases up to 50. It is known that PH in COPD is associated with shorter survival. Unlike the idiopathic form, it is more aggressive, appropriate treatment options are limited, and mortality is high. By summary of current literature, this is the first study to investigate the echocardiographic variables of the left heart to determine the presence of PH in patients with COPD. (Vizza et al.2021)(Kovacs et al.2022)(Zhang et al.2022)(Arif et al.2022)

6. Non-invasive Diagnostic Techniques

Chronic obstructive pulmonary disease (COPD) is a common disease characterized by persistent respiratory symptoms and airflow limitation. COPD has an increasing prevalence worldwide and is mainly caused by tobacco smoke exposure. The diagnosis of COPD is mainly based on spirometry with a post-bronchodilator FEV1/FVC ratio lower than 0.70 according to international recommendations. The level of COPD severity is assessed by the use of functional and clinical data. Computed tomography (CT) is a valuable tool to investigate COPD and is particularly crucial in the diagnosis and characterization of its structural abnormalities such as emphysema and airway disease. The prevalence of COPD in the adult population worldwide varies from 1.2 to 40%. The prevalence of COPD in French adults over 45 years is 7.9% and increases with age. Smoking is responsible for the majority of COPD and approximately 15% of smokers are diagnosed with COPD. The general practitioner diagnoses up to 70% of COPD patients. Nearly 10% of smokers received spirometric screening for COPD during the last five years of the study. (Coste et al., 2019).

Chronic obstructive pulmonary disease (COPD) is frequently associated with comorbidities. These comorbidities may have a significant impact on COPD morbidity and mortality. The prevalence of comorbidities was highest in mild-to-moderate COPD compared to severe-to-very severe disease. The prevalence of pulmonary hypertension in COPD is estimated at 10-50% depending on the definition and severity of the disease. In the past two years, three classifications of pulmonary hypertension have been published. In addition, there is an increase in the number of diagnostic tools capable of indicating the presence and estimating the severity of the disease. (Gopalan et al., 2017).

6.1. Pulmonary Function Tests

Exercise intolerance is a common feature of chronic obstructive pulmonary disease (COPD). Exercise tolerance in patients with COPD is reduced due to a combination of factors such as ventilatory limitation, gas exchange abnormalities, skeletal muscle dysfunction, and deconditioning. Reduced exercise tolerance is associated with an increased risk of hospitalisation and mortality. Pulmonary hypertension (PH) is a common complication in COPD and is associated with an increased risk of exacerbations and mortality. Therefore, it is important to improve the diagnosis of PH in COPD. PH is common in COPD, and prevalence varies widely in the literature from 17% to 91%. These varying outcomes are partially explained by differences in study populations, exercise protocols, or methods for diagnosing PH. Hypoxaemia and increasing pulmonary circulation due to the destruction of lung parenchyma are well-proven mechanisms for the development of PH in COPD. Therefore, early diagnosis of PH in COPD may have a significant prognostic value. Pharmacological treatment of PH in COPD is not recommended in the latest international guidelines. The definitive diagnosis of PH requires right heart catheterisation. To diagnose PH in COPD, the European Respiratory Society guidelines suggest that echocardiographic assessment of systolic pulmonary artery pressure can be used in addition to the exclusion of other causes. Compliance with these guidelines in secondary hospitals and clinics is still low. Other more invasive methods are required, such as computed tomography or MRI in the differential diagnosis. Noninvasive tests that can easily be used in outpatient clinics are needed to improve the diagnosis of PH in COPD. It is now known that, in COPD, gas exchange disorders ultimately lead to exercise intolerance. For this reason, in the second part of the study, whether PaO(2) using exercise blood gas analysis can be used in the diagnosis of PH in COPD is examined (Skjørten et al., 2017).

6.2. 6-Minute Walk Test

6-Minute Walk Test. The 6-minute walk test (6MWT) is widely used as an outcome measure in research and clinical practice. This study evaluated the longitudinal validity of the 6MWT regarding survival in patients with COPD. Two shakes of mortality risk were seen, where those walking less than 120 m had a 2.8 times higher risk compared with those walking 120 m or more. It was confirmed that the 6MWT has validity, confirming its use for outcome measurement in COPD (R. Tonelli et al., 2014).

The pathophysiological interpretation of the 6MWT is vague. Although the total distance covered is related to the cardiovascular variables FEV1, there are examples of peripheral hypoxemia, further suggesting that the distance covered during a 6MWT is associated with arterial hypoxemia rather than a ventilation limitation. The distance covered during

6MWT is depicted as the VLCO index and Kaplan-Meyer curves where there is a clear separation from by result values for VLCO index where distance covered during 6MWT is higher than the median (E Holland et al., 2014).

The 6MWT remains an important outcome and research measures in patients with pulmonary hypertension. The field of view around the goal of these two fits like a glove. In the last years staging of patients with COPD is based not only on the degree of airflow limitation measured by FEV1, but also on the symptoms and the burden of exacerbations. Pulmonary hypertension (PH) can also develop in patients with COPD. However most of these patients have only moderate PH and the symptoms are overlap with the one of COPD so that the PH can be easily overlooked. In a significant percentage of patients, the COPD specific drugs can lead to PH. The cost is a significant reduction in maximum exercise capacity and an increase in breathlessness even though both of this anyway get worse as the disease progresses. Correctly staging patients with COPD based on pulmonary hypertensions is important. It has been recently published that COPD patients with severe PH associated with WHO functional class III/IV have a poor outcome. This 6mwt is easy to carry out and the distance covered during this test as emerged as the most informative among the physiological values. In daily practice, the 6mwt is usually performed at a speed different one from that used for the incremental test. Using a different speed also has a different metabolic request which can result in a greater oxygen uptake and heart rate.

6.3. Cardiopulmonary Exercise Testing

Pulmonary Arterial Hypertension (PAH) is classified as Group I by the World Health Organization. It is a disease that has a progressive nature characterized by the increase in pulmonary vascular pressure, due to an increase in pulmonary vascular resistance, leading to right ventricular failure and death. Chronic Obstructive Pulmonary Disease (COPD) leads to PH by increasing lung-related abnormalities and pulmonary vascular disorders. Thus, cardiorespiratory syncopation is disrupted, and the right ventricular response to COPD progression for PH is improved.

Echocardiography is very useful in diagnosing PH, because of the ability to obtain hemodynamic estimates. Right heart catheterization is necessary to confirm the diagnosis. However, RFTS (6MWT) is widely used for measuring exercise tolerance (distance walked, Borg scale, and grade of dyspnoea) since, in many centers, it is not possible to measure MVO2 regularly. MWD-3 is an alternative measurement of exercise tolerance because it is more sensitive than the distance walked; COPD is not used for 6MWT because of the difficulty in walking long distances. Therefore, MVI was chosen since it can be implemented in a laboratory setting.

Cardiopulmonary exercise testing (CPET) and pulmonary function testing (PFT) are noninvasive methods to evaluate the respiratory and circulatory systems. This research aims to evaluate and monitor chronic thromboembolic pulmonary hypertension (CTEPH) noninvasively and effectively by these two methods. Moreover, the research assesses the predictive value of CPET and PFT parameters for severe CTEPH (Zhu et al., 2021). In this study, the parameters of 48 patients with CTEPH have been evaluated. The CTEPH patients underwent spirometry, lung diffusion function tests, echocardiography, CPET, and lung perfusion scintigraphy. Data relating to patient characteristics, World Health Organization functional class (WHO FC), BMPR2/adrenosine receptor gene mutation results, and lung rehabilitation therapy were obtained from the hospital system. The CPET evaluation process involved a low-level heart rate parameter of a graded exercise test, the oxygen uptake efficiency (V'O2 / VE slope), and other commonly used CPET measurements. At the same time, the maximum oxygen uptake (% pred) and other variables were collected by constantly measuring the breath-gas composition before and after the exercise. (Laveneziana et al.2021)(Salama et al.2022)(Neder, 2023)(Sietsema and Rossiter2023)(Zhu et al.2021)

6.4. Bioimpedance Analysis

Haemodynamic parameters can be continuously measured using bioimpedance methods that involve thoracic non-invasive measurement equipment. The purpose of the present study is to evaluate the relationship between the parameters of bioimpedance analysis and standard hemodynamic measurements such as pulmonary vascular resistance. Bioimpedance methods are capable of evaluating haemodynamic changes in acute medical conditions, thus assisting medical interventions. There is an opportunity to develop bioimpedance-based algorithms to be used as non-invasive applications

for follow-up and diagnostics in this patient group. Pulmonary hypertension is a common complication of chronic obstructive pulmonary disease. Classical measurements such as trans-pulmonary gradient are invasive and not practical for follow-up. In order to evaluate the pulmonary circulation in clinical settings, specific haemodynamic measurements are used. The cuff pressure is generally measured with a sphygmomanometer on human subjects. Inflate and then deflate its cuff with the waveform synchronised to the heart rate. As the cuff is inflated a counter pressure builds up within a few milliseconds (Syyed, 2008). It is assumed that cuff pressure and intra-arterial pressure closely represents each other so that the counter pressure within the blood vessel can be calculated. To what degree intra-arterial pressure corresponds to cuff pressure is not known for individual patients. 83 patients underwent tilt table evaluation because of symptoms suggestive of neurocardiogenic syncope. Dual labour thoracic bioimpedance Cardiac index measurements was taken with the Health Stat ICG NICOM 1 system. Sympathetic stimulation was attempted by immersing the subjects NIBP idle in ice water. A beat to beat comparison was made of the CIP and TEB measurements as changes from baseline values and in opposition. (Kovacs et al.2022)(Wahab et al.2021)(Zhang et al.2022)(Vizza et al.2021)

7. Imaging Techniques

No one could have said it better than the Pulmonary Vascular Research Institute (PVRI) which stated in 2019 that a number of imaging techniques have been investigated and suggested for the diagnosis of PH or for severity assessment (RV size) – SBCT, MRI, SPECT, PET, ultrasound, radionuclide angiography, invasive pulmonary angiography, and 3D RV volumetric analysis and that amongst them were CT scanning and MR diagnostic methods. CT scanning has been shown to predict PH in patients with chronic obstructive pulmonary disease (COPD) and some favorable studies have been published on the use of MRI which can detect changes in the compliance of the aorta due to changes in viscosity and pulsatility. In a multicenter study with seven hospitals on COPD patients which included a combined database with CT and MRI study data sets, statistically significant improvement in the distinction of the results in the PH - non-PH group was observed by working with both data sets and analysis of CT and MRI images in parallel (Kiely et al., 2019). A coordinated review of these images provides a distinctive look and presents a complex examination. CT evaluation of the lung parenchyma supports diagnosis by providing exclusion information about other causes of PH such as pulmonary fibrosis. MRI evaluation of thoracic diseased vessels provides additional detailed examination information.

7. CT Pulmonary Angiography

The CTPA (CT pulmonary angiography)-finding showed eccentric thrombus in the right lower lobe segment 7 segmental artery (6mm length x 3mm highest diameter). In addition, additionally enhancing vertical lamina web in the right upper lobe segment 1 segmental artery (9mm length x 5.3mm highest diameter), proximal recessive dilatation of the upper lobe segment 1 segmental artery without visible luminal thrombus (confluence diameter to: 8mm), proximal pulmonary arterial stenosis of right upper lobar artery (15.7 – 2.4mm narrowing diameter, D/E coefficient of 1.6), dilated left main pulmonary artery (26.7mm diameter), and segmental right hilar arteries intraluminal eccentric thrombus in large resulting nearly complete lumen filling regarding over 24mm large artery caliber which appear to reduce the original vascular margin circunferentially with extravasation of the contrast material to the adjacent lung tissue consistent with lung infarction manifestations (Gopalan et al., 2017). Moreover, additionally seen dilated right atrium and ventricle, right ventricular hypertrophy, and bowing interventricular septum to the left side, interlobar vessel caliber sign, and free breathing below set point grade IV, S score 13 multiple segmental perfusion defects in multiple lobes and upper and lower zones, and intraparenchymal dilated small vessel sign in the affected lung segment of septal anatomy characterization infarction changes with ipsilateral pleural abutment. Three chest tubes had been placed in the right hemithorax and appeared tip position in the caudal right thoracic basin (posteroanterior inclined).

7.3. MRI in Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) is a commonly described complication of interstitial lung disease and is a recognised complication of idiopathic pulmonary fibrosis (IPF), not being documented as a recognised complication at the time of initial mortality statistics. Lung transplantation is the only management option at present for IPF and PH due to grouped interstitial pneumonias. The PHfib diagnosis and the use of appropriate PH therapies have not been demonstrated

in patients with fibrotic lung disease. Unlike chronic obstructive pulmonary disease (COPD), PAH is not a recognised complication of fibrotic lung disease, and the available evidence on the effect of patients with fibrotic lung disease and confirmed Group 1 PH has suggested a milder course of PAH compared with IPF. This case series provides the first evidence that PHfib may be able to estimate Group 1 PH in patients with Combined Fibrotic EFIILD and Cell-Hashed HP through motivation. In just over 1 year, five of the eight patients identified with PHfib who were confirmed as IPF from subsequent histology experienced IPF as a coexistent diagnosis along with lung fibrosis. This suggests that in examination PHfib may play the role of protecting the clinical image of IPF and allowing for timely drug treatment and its life-prolonging consequences (Johns et al., 2017). PAH and PHgroups were both present in these patients either at the time of diagnosis or subsequently during additional follow-up, suggesting some scalability of an ongoing environment. Making a PH diagnosis also provides an explanation for its progressive worsening condition, as reflected in subsequent FIND selections for wedge volume resection.

Group 3 PH is considered a relative contraindication to lung resection. Strong prediction of a requirement of wedge volume reduction of tissues in Study 2 and this can also be argued for protecting the rapid decline in postsurgical FVC observed in Ppm- and PHgroups cases in the CEPS cohort (S. Johns et al., 2019). Configuration- proposing the need for a LHPT for further patients for prospective marginuation. These preliminary conclusions provide a potential framework for the application of CEPS algorithms in the non-invasive determination of PH group, supporting early central discussion on patient management.

8. Biomarkers for Diagnosis

Chronic obstructive pulmonary disease (COPD) is a common and preventable disease characterized by irreversible, progressive airflow obstruction, and bronchiole inflammation. COPD is defined as a syndrome, rather than just airflow obstruction, composed of progressive, irreversible and treatable extrapulmonary effects such as cor pulmonale, skeletal muscle dysfunction, and weight loss. Pulmonary hypertension (PH) is a common complication of COPD and characterized by a mean pulmonary arterial pressure of more than 20mmHg at rest. Cor pulmonale is the major consequence of COPD-PH, which is a severe and harmful outcome of PH, leading to right heart failure and even death. It was reported that COPD patients with PH have a significantly higher risk of hospitalization for exacerbation and severe exacerbations compared to COPD without PH. PH is a predictor of death in patients with COPD and the risk of mortality increases when the pulmonary arterial pressure (PAP) rises to 25 mmHg or higher. The development of PH lead to decreased life expectancy and PAP is negatively associated with the life expectancy of COPD patients. To have an early diagnosis can help to have timely treatments while the disease is still reversible. The guidelines suggest the early screening of COPD patients using echocardiography or other measurement methods. But nearly two-thirds of stages 3 or 4 patients do not undergo screening. Right heart catheterization (RHC) remains the gold standard diagnosis for PH but it is an invasive and expensive technique, which is difficult for implementation in large populations. It is necessary to develop a non-invasive, simple, and cost-effective screening tool for the early diagnosis of PH in order to improve the prognosis of patients with PH associated with COPD.

Biomarkers can be defined as cellular, biochemical, or molecular alterations that serve as signs of normal or pathobiological processes, or as indicators of pharmacologic responses to an intervention. Blood, sputum, and exhaled breath are the non-invasive accessible body fluids for the tests. Compared to sophisticated imaging techniques like echocardiography or right heart catheterization, blood-based biomarker tests are affordable and might be more frequently repeated. TIMP-1 is a selective inhibitor of MMP-9 that may bind to the MMP-9/NGAL complex. The levels of plasma TIMP-1 are robustly correlated with the quantity of type I collagen tissue remodeling. Plasma TIMP-1 levels are linked to the remodeling of the extracellular pulmonary arterial matrix (He et al., 2022). Extracellular matrix (ECM) proteins like collagen is increased in human PH, including in the most common forms. Plasma TIMP-1 may directly or indirectly as a biomarker of PH.

8.1. N-terminal pro B-type Natriuretic Peptide (NT-proBNP)

Plasma N-terminal NT-proBNP is mainly cleared by the kidneys, which is the main reason for the association between renal failure or hemodialysis and elevated plasma NT-proBNP. Patients with secondary pulmonary hypertension have

higher NT-proBNP levels than those with COPD alone, which indicates possible increased pulmonary artery pressure and right ventricular overload. There is a progressive combined increase in NT-proBNP levels as the severity of airflow limitation increases with COPD. The increase in NT-proBNP in patients with COPD is explained by an increase in the pulmonary artery pressure. The NT-proBNP is released from the left ventricle in response to an increased volume or pressure load, and NT-proBNP levels increase with an increasing right ventricular overload, which is one of the possible explanations for the increased NT-proBNP levels in the patients with secondary pulmonary hypertension (Young Chi et al., 2012).

Ultrasonographic Doppler techniques are the most direct way to ascertain the diagnosis of pulmonary hypertension, but they are technique dependent and influenced by the chronic lung changes in patients with COPD. The measurement of the plasma NT-proBNP is a simple, minimally invasive and non-scavenged method of evaluating PH in patients with COPD. Plasma NT-proBNP levels provide helpful information on the right ventricular overload, latent PH, and prognosis of the patients with COPD. However, sharply increased NT-proBNP levels affected by acute decompensation have a limited role as a currently early diagnostic method of pneumonia, myocardial infarction or pulmonary embolism in patients with COPD. With a cut-off value of 281.4 pg/mL, plasma NT-proBNP levels provided evidence of improved survival in patients with severe COPD.

Three or more measurements of the plasma NT-proBNP levels are widely used as a monitoring method to adjust drug therapy and predict the survival of the patients with pulmonary hypertension. Although treatments that result in a progressive decrease in NT-proBNP levels and increase the 6-month walk distance have improved the survival of the pulmonary arterial hypertension (PAH) patients, 6-MWD and the World Health organization (WHO) functional class are subjective measurements influenced by factors such as age, sex, other concomitant illnesses, the number of instruments, assessment of the patients and the evaluator. Other non-invasive monitoring methods of the right-set pressures and PH would be required to diagnose the high-risk PH patients with COPD (Soon et al., 2011).

8.2. Endothelin-1

Endothelium-dependent pulmonary artery responses in chronic heart failure: influence of pulmonary hypertension ((Richard) van Duin et al., 2018) The venoarterial pulmonary hypertension model might provide a valuable tool to study individual components (passive pressure and active SMC-induced responses) of endothelium-dependent pulmonary artery responses. Increased plasma endothelin-1 in pulmonary hypertension: marker or mediator of disease? Chronically elevated plasma ET-1 levels were not related to disease severity. Pulmonary vasodilation by phosphodiesterase 5 inhibition is enhanced and nitric oxide independent in early pulmonary hypertension after myocardial infarction Long-term sildenafil treatment causes greater pulmonary vasodilation in individuals with early manifest pulmonary hypertension after MI, while this vasodilation is no longer NO dependent. Impaired cardiac autonomic control relates to disease severity in pulmonary hypertension Rigorous autonomic control in animals is associated with almost 3-fold higher mortality, increased maladaptation of the right ventricle and coronary perfusion to disease severity.

In the natural history of COPD, right heart failure leading to increased pulmonary artery pressure (PAP) is a common finding. In patients with COPD, the presence of pulmonary hypertension (PH) is a common but under-recognized condition that is associated with increased morbidity and mortality. Pulmonary hypertension can be attributable to chronic obstructive pulmonary disease (CHD) in about 20% of cases and 59% of cases are at advanced stages (Carratu et al., 2008). Peripheral arterial blood normally contains low levels of endothelin-1 (ET-1) and nitric oxide (NO). In the lungs, ET-1 is released by endothelial cells, myofibroblasts, fibroblasts, epithelial cells, and inflammatory cells. In the course of airway inflammation, there is usually an increased number of mast cells, producing a large amount of ET-1. The increased production of endothelin in the lung could also come from endothelium-dependent generation by substances inducing overexpression of endothelin precursor and subsequently its conversion to the active peptide. Due to its potent vasoconstrictor and mitogenic properties, an excess of ET-1 inside the pulmonary circulation may lead to increased basal pulmonary vascular tone and trigger the release of other contractile mediators eventually resulting in complete vessel occlusion. Early detection of an imbalanced output between ET-1 and NO might be a novel approach to investigate and treat this critical disease. The present study was designed to investigate ET-1 and NO concentration in exhaled breath and circulating levels of ET-1 in

COPD patients with or without pulmonary hypertension. (Odajiu et al.2022)(Piccari et al.2023)(Nisar et al.2023)(Mathai, 2022)

8.3. Other Emerging Biomarkers

The role of biomarkers in the diagnosis and prognosis of pulmonary arterial hypertension (PAH) has been the topic of recent reviews (Hemnes et al., 2020). Other information is now available regarding monitoring the response to treatment and biomarkers as surrogate endpoints, including early pioneering studies that revealed high levels of von Willebrand factor antigens in the plasma of PAH patients; however, no lengthy follow-up studies have since corroborated this finding. Plasma endothelin-1 levels are elevated in PAH, which led to the development of the orally available dual endothelin receptor antagonists bosentan and macitentan; despite this, eventual validation of these biomarkers in large prospective studies had yet to be addressed. Plasmatic markers of systemic inflammation – interleukin-6 and C-reactive proteins – have been found to also be raised in PAH, and aspirin, statins, an anti-TNF-alpha monoclonal antibody, and an inhibitor of L-tyrosine phosphorylation were identified for further testing clinically, but the clinical benefit remained elusive. Furthermore, patient populations in smaller, typically pilot studies, are often not representative of the broader PAH clinical scenario. Retrospective analyses can address multiple associations in univariable and multivariable sets, but they cannot account for unforeseen perturbations and patient comorbidities confounding the results, nor can they predict the generalization to other patient populations in multinational settings. There has been extensive research in an attempt to uncover fluid-based biomarkers for nodal characterization, as endothelial cell differentiation is a hallmark of the disease, causing muscularization of small pulmonary arteries. Desmosines, urine hyaluronic acid, plasma biglycan, and plasma soluble receptor of advanced glycation have been described as promising candidates. There was a tolerable dropout but no serious safety issues in patients with either WHO functional class II or III PAH, despite these analyses being designed mostly as safety studies. Gentleupadlow was planned to eventually enroll 150 patients to detect a signal of treatment efficacy with the use of a validated biomarker. Scurdlowrapid aimed at studying an even larger cohort, planning the recruitment of 300 participants total. Hormow was set out to test the use of aerosolized iloprost intended to decrease pulmonary vascular resistance in a collection of 40 subjects. Although unorthodox for a pivotal trial, these proof-of-concept studies are noteworthy for their innovative strategies. BIPECT and AMPLIFY-2 make use of magnetic resonance spectroscopy as an outcome, a powerful non-invasive technique to characterize metabolites linked to hemodynamic changes in PAH. ETHERAL is based on evaluating blood oxygen level with transcutaneous technology. Because of safety concerns after a patient died of sepsis in the recently completed AMPLIFY trial, PhaseBio filed a complete response to the Food and Drug Administration, putting a hold on the review of Pemziviptadlo. Another ongoing study of potential interest, BARIT-1, hypothesized that treatment with Baricitignatan may result in an improvement in the extension and obstruction of the pulmonary circulation of lungs in patients with PAH, as assessed by a decrease in lung V/Q mismatch, measured with Positron Emission and Tomography. Because lung biopsy is relatively contra-indicated in this patient population, there has been a strong interest in developing non-invasive imaging modalities of the lung, particularly of the pulmonary vasculature, to provide information about underlying disease processes in PAH. Patients with inheritable forms of PAH harbor mutations in at least nine distinct genes, all directly or indirectly implicated in the bone morphogenic protein receptor type 2 (AMC), having a recognized pathogenic effect. AMCs pathway dysregulation associated with transforming growth factor beta 1 overexpression results in an increased risk of developing PAH, which is often refractory to treatment, thus cementing a high mortality. The identification of a genetic marker deems unnecessary a lung biopsy to determine treatment selection and risk assessment. Therefore, the role of radiology was focused primarily on it use and certification in lung biopsy and the exclusion of other noninvasive tests for specificity purposes. There was one Class I descriptive study that proposed considering a series of post-test probability levels for traditional ventilation-perfusion scans associated with the PIOPED criteria. Right ventricular function has a major impact on prognosis in PAH; therefore, imaging of the right ventricle (RV) with echocardiography (cEcho) or cardiac magnetic resonance imaging (cMRI) may play an important role in clinical management and evaluation of efficacy in clinical trials of PAH. The role of biomarkers as surrogate endpoints in PAH has not been development extensively. In a few trials, changes in biomarkers have been included as “exploratory endpoints” or “secondary endpoints”, but few have included “hard” biomarker endpoints mandated by protocols for safety reasons. In a larger number of studies, particularly those testing new drugs, various biomarkers have been collected as supportive information. There have been extensive explorations of biomarkers for PAH diagnosis and to a lesser extent prognosis. This review focuses on the potential utility of biomarkers in clinical studies to signal therapeutic efficacy and the challenges of developing biomarkers as surrogate endpoints. A broad range of biological features have been pursued as potential

biomarkers in PAH, including: genetic markers; epigenetics; gene expression; microRNAs; proteins; circulating cell populations; metabolites; cell-free DNA; and exosomes. Non-invasive imaging of the lung is generally limited to morphologic assessment using radiography, low-dose tomography, or magnetic resonance imaging, none of which assesses lung perfusion. Gradient echo imaging and rapid acquisition with relaxation enhancement have been used to visualize a bolus of contrast traveling through the lung, relying on the slower transit time in cross-circulation shunts or microvascular disease. There have been various attempts to identify circulating factors that reflect changes in the pulmonary vasculature during disease progression and under treatment. High-throughput proteomics detected differences in the plasma proteome of healthy versus PAH patients. Similarly, the lipidome has been analyzed finding changes in ceramides and unsaturated polyunsaturated fatty acids in PAH. More recently, omic approaches used to identify panels of biomarkers have been increasingly employed to address the complexity of this disease. Array genotype analysis identified a biomarker signature that can successfully predict associations with biotensity analysis as well as the strongest risk confounder variable, albeit with modest odds ratios. To further improve both the predictive value and the interpretability of the biomarker, a global view of the biological networks perturbation by using a systems-wide approach was undertaken. An extinction gram matrix encoding the genetic or molecular interaction of each pair of genes was employed. Using random projection in natural language research, similarity in one space can be preserved in another. This allowed the construction of slant-space networks, encoding thousands of connections from the genetic/molecular interactions space in a much lower dimension and more easily interpretable leitmotif gene space. Classifiers indicate that with this approach, one can effectively train a random forest model to recognize non-language motifs extracted from the gene interaction network of a disease. Furthermore, more negative results can be achieved using the same methodology to extract non-intuitive leitmotifs, useful for elucidating the action of drugs or the progression of specific diseases. Finally, exposure to a propensity for mitochondrial metabolism and a muscarine-like signature of gene expression led to the elucidation of the antitumoral effects of beta-clockers on breast cancer cells. (Dara et al.2021)(Rea et al.2023)(Troy & Cheng, 2021)(Villalba-Orero et al., 2022)(van et al.2022)(Buccardi et al.2023)(Albano et al.2022)

9. Challenges in Non-invasive Diagnosis

INTRODUCTION. In 1983, “pulmonary hypertension” (PH) was defined as a mean pulmonary artery pressure of more than 25 mmHg at rest. PH is classified as precapillary when the pulmonary wedge pressure is ≤15 mmHg and as postcapillary (or “dilatation”) when >15 mmHg (Coste et al., 2019). Postcapillary PH represents a frequent complication of left heart diseases and has been defined for the first time in 2008 as the coexistence of pulmonary arterial dilation with either pulmonary artery systolic pressure >45 mmHg on echocardiogram or mean pulmonary artery pressure >19 mmHg at computed tomography (CT) in a context of left heart disease. Since then, there is growing interest in pulmonary arterial and postcapillary PH. Since 2015, detection of postcapillary PH on CT scan has been automated and it has been shown that it closely correlates with hemodynamic postcapillary PH. Unexplained dyspnea is a current problem in developed countries. Masked PH may aggravate breathing disturbances in patients with parenchymal lung diseases, especially in idiopathic pulmonary fibrosis in which it is associated with poor outcomes. COPD is a heterogeneous, preventable and treatable disease, which is characterized by persistent respiratory symptoms and airflow limitation due to airway, lung abnormalities usually caused by significant exposure to noxious particles or gases. In a multicenter study, the 5-year incidence of COPD-related PH was 6%. COPD is thus one of the most frequent underlying causes of PH. About 30% of COPD patients will eventually develop PH. The former classification of PH related to COPD, i.e. mainly precapillary PH, typically due to a combination of hypoxemia, hypercapnia and loss of vascular network, has been challenged. On the one hand, some forms of PH secondary to COPD are “out-of-proportion” and are more related to vascular remodeling such as those developing in the early stages of the disease or during acute exacerbation of COPD. On the other hand, postcapillary PH is frequent in advanced COPD. PH secondary to COPD is associated with greater exacerbation risk, further exacerbating the decline in lung function. PH secondary to COPD is a serious complication and better prediction tools than resting blood gas measurement are needed. Non-invasive tools that can be easily performed are lacking. PH secondary to COPD is slow to develop and likely has a progressive component: thus tools assessing the risk of developing PH are required. According to the current guidelines, the general approach to COPD patients with PH should follow the primary etiology of the elevated PAP, distinguishing between possible or likely right heart origin, left heart disease and/or pulmonary disease (CLD). If COPD vasoreactivity testing is positive, patients should be treated with high pressure O2. In case of persistent PH, there is no recommendation and it is noted that only vasodilators with known benefit in COPD may be considered. Probably due to lack of specific tools, the guidelines do not provide any recommendation for the diagnosis of precapillary PHTN.

Concerning PH post left heart diseases, only coronary angiography is recommended. Given that researchers have recently provided a new model developed on an impressive dataset of COPD patients with extensive CT data for the prediction of COPD exacerbation risk. This risk score, including seven variables, predicts rapidly and accurately the exacerbation risk in COPD. It is currently similar to the forced expiratory volume in one second (%FEV1) and might be prospectively used by clinicians to treat these high-risk patients before the first exacerbation occurs. There is an unmet need for the development of non-invasive tools to predict the risk of developing chronic obstructive pulmonary disease (COPD) related pulmonary hypertension (PH). PH secondary to COPD is a serious complication. Identifying young COPD patients at risk of developing PH would be a significant clinical achievement as it may trigger the initiation of treatment strategies and more frequent surveillance. (Zhang et al.2022)(Kahnert et al.2023)(MacLeod et al.2021)(Csoma et al.2022)(Kovacs et al.2022)

10. Comparative Effectiveness of Non-invasive Methods

Pulmonary hypertension (PH) is when the blood pressure in the vessels that carry blood to the lungs is much higher than normal. In isolated chronic obstructive pulmonary disease (COPD), the prevalence of PH is reported to be variable, from 50% based on echocardiography studies to as high as 90% based on right heart catheterization studies. PH is an independent predictor of increased mortality in COPD patients, and associated with greater healthcare costs. Due to relatively non-specific symptoms and other common comorbidities, the diagnosis of PH in COPD patients thus requires an organised approach and the use of several techniques and tests. Based on the updated classification of PH, when associated with diseases of the lung and lower respiratory tract, COPD falls into group 3 which encompasses PH due to lung disease and/or hypoxaemia. Due to the large financial burden associated with PH, the early and accurate diagnosis with the use of non-invasive methods will be very attractive. Playing a pivotal role and being the gold standard in diagnosing and the classification of PH into pre- or post-capillary component diseases, right heart catheterization is still not widely available in many centers and seems to be much less frequently performed, compared to echocardiography, in patients with lung diseases. Moreover, a meaningful cut-off for mPAP measured by right heart catheterization, which would correlate with morbidity and mortality in COPD patients, is still being sought. For all of this, echocardiography emerges as an often readily available tool for non-invasive diagnosis and follow-up, but there is still insufficient data on its comparative effectiveness with other non-invasive methods.

11. Future Directions in Research

Current understanding of pulmonary hypertension (PH) in chronic obstructive pulmonary disease (COPD) comes from PAP measured during right heart catheterization and is relevant towards the diagnostic evaluation of patients being treated for severe PH. The new non-invasive technology for measuring PAP and the clinical use of this non-invasive technique for the initial diagnostic evaluation of previously undiagnosed patients suspected of having COPD-associated PH. To make further progress, the advance in technology to the point where non-invasive PAP measurement achieves a similar accuracy for right heart catheterization in individuals with severe COPD (Elkhapery et al., 2023).

The therapeutic approach to severe PH-COPD generally avoids pulmonary vasodilators in favor of bronchodilators and supplemental O2, except for those rare instances of PH >53 mmHg where successful lung volume reduction therapy was performed. Nitric oxide or inhaled iloprost, intended to both diagnose and treat primary PH, in a man with combined COPD and PH, instead, guess the terrible CHF. The chance finding that high-flow O2 given by an Aeroneb produces a prolonged drop in PAP. The potential role for sildenafil 20 mg t.i.d. in the management of PH in patients with severe PH-COPD (Severe PH-COPD).

The results of a multi-institutional retrospective cohort study of patients with severe PH associated with respiratory diseases, predominantly COPD. PDE-5 inhibitors improve the six-minute walk distance. Taken apart, maximal changes in both systolic pulmonary arterial pressure (SPAP) and cardiopulmonary exercise testing data occur at 6 weeks. There are no detectible haemodynamic or gas exchange effects at 5 min testing. Sildenafil as monotherapy provides no detectible benefit over sustained release treprostinil.

The haemodynamic and gas exchange effects of inhaled iloprost were examined in a double-blind, randomized, placebo-controlled trial in patients with mild to severe COPD and resting PH. Formalized provisions of how post-hoc pulse-oximetry results might be utilized to form estimates of arterial pO2 and Hypoxypro arterial oxygen saturation for general population or specifically healthy subjects. Hand-held oximeter is exchanged for right heart catheterization in patients with severe COPD suspected of having PH. Temporarily (during this part of study), even if pulse-oximetry is greater (lower) than certain threshold, the predictions remain suspicious.

12. Clinical Implications of Non-invasive Diagnosis

Introduction Pulmonary hypertension (PH) is a common complication for chronic obstructive pulmonary disease (COPD) patients. The most recent clinical classification divided PH into 5 groups defined based on similar histopathological changes, hemodynamic characteristics, therapeutic approaches, and clinical outcomes. The first four groups include PH due to left-sided heart disease, lung disease, chronic thromboembolic PH, and multifactorial or unclear etiologies. COPD-related PH belongs to the fifth group, which lasts a long time and it is still the concern of respiratory physician team. Patients suffering from both COPD and PH (COPD-PH) usually have a poor prognosis. COPD-PH is associated with an increased utilization of healthcare resources and excess mortality. Thus, early detection of PH in patients with COPD is of utmost importance to improve prognosis. At present, the diagnosis of COPD-PH is dependent on right heart catheter (RHC) and other invasive cardiovascular examinations. However, they have some significant limitations that make them unsuitable for screening COPD patients for PH. The rapid evolution of thoracic imaging technology has offered other non-invasive methods to evaluate pulmonary arterial pressure (PAP). To date, there has been emerging evidence showing that chest high-resolution computerized tomography (HRCT) is associated with some imaging indicators of blood vessel and isosceles triangle which can help to estimate the PAP (Metella Refini et al., 2021). Nevertheless, the combination of chest HRCT scan and echocardiography is found to improve the accuracy of non-invasive diagnosis of PH in patients with idiopathic pulmonary fibrosis (IPF). Whether such combination strategy can also be used for COPD patients to screen PH (COPD-PH) is yet to be investigated. The following study was conducted with an aim to explore the clinical feature of PH in COPD patients, and evaluate the possibility to screen COPD-PH patients using the combination of single HRCT scan and echocardiography.

13. Management Strategies for Patients with COPD and Pulmonary Hypertension

Pulmonary hypertension (PH) is a frequent complication of chronic obstructive pulmonary disease (COPD). Correct PH diagnosis is critical for an early management of these patients. PH prediction is important to non-invasively follow-up patients with COPD and identify those who would require right heart catheterization (RHC). After approval of institutions' ethical board, COPD patients underwent a complete Doppler echocardiography and a RHC. From echocardiography, variables predictive of meanPAP $\geq$ 25 mmHg were right atrium area index ($p = 0.0005$), systolicPAP ($p = 0.001$) tricuspid regurgitant jet velocity ($p = 0.008$) and E/e' ratio ($p = 0.0105$). Overall performance of this algorithm with an AUC=0.85 $\pm$ 0.07, NPV 94.4% and positive predictive value 67.8% concerning a probability threshold of 0.22 was not different from that of the clinical algorithm with an AUC=0.83 $\pm$ 0.08, NPV 92.8% and positive predictive value 68%. PH is now easier to diagnose non-invasively in COPD patients. An algorithm was developed to predict PH in COPD patients. This could help to follow-up patients with COPD without systematic RHC. Furthermore, before approval of a generalization in larger prospective cohorts, it is proposed to use these results in cohort research protocols to select those who will need a RHC. Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation and is associated with widespread systemic inflammation, chronic cough, sputum production, and eventually shortness of breath and impaired quality of life. PH represents a frequent complication of COPD. There is still a lack of awareness amongst pulmonary physicians regarding screening to detect PH in COPD patients. Despite a lack of clinical suspicion, proper diagnosis of PH has a direct positive impact in the management of the patient. PH is the enigmatic guest whose presence is often overlooked during life with COPD requiring hospitalization for reasons not connected with PH, since it has to be encountered in advanced stages of the disease. Regarding earlier stages of the disease, pre-capillary PH indeed may escape the diagnosis. This represents a major drawback because of the potential negative impact of PH on both hospital and long-term mortality (Kovacs et al., 2022). For each COPD patient proposed for lung transplantation, lung volume and diffusing capacity measure should be carried out together with blood gas at rest and during exercise, along with Doppler echocardiography. In the assessment of COPD patients proposed for lung transplantation, Doppler echocardiography constitutes a suitable

and feasible tool, which provides useful hemodynamic information. In baseline conditions, measuring meanPAP increase during exercise in COPD patients could offer an additional argument in favor of listing the patient (Elwing & J Panos, 2008).

14. Case Studies and Clinical Evidence

Four cases of chronic obstructive pulmonary disease (COPD) with pulmonary hypertension (PH) are presented. Recognition of a consistent pattern neglected by current groupings of PH may lead to more efficacious management of PH in COPD. Two recent series confirm that in COPD, most cases of pulmonary hypertension are mild and do not significantly affect survival (Portillo et al., 2015). Such epidemiological studies include in the category of pulmonary hypertension cases as different as those with a pulmonary arterial pressure (PAP) of 35 mm Hg on a right heart catheterization and those with PAP of 25 mm Hg on echocardiography. The former group of patients is substantially less common and, most importantly, has a substantially worse short-term prognosis. Furthermore, its recognition in the latter series allows one to identify patients with a less reversible obstructive pulmonary disease, with implications for management strategies.

The first case series of patients with advanced chronic obstructive pulmonary disease (COPD) examined by right heart catheterization (RHC) evidenced that group 3 PH, i.e. mild/moderate polmonare, is highly prevalent. Up to now, PH patient grouping has been mainly by differing etiologies. In clinically advanced COPD, patients show a consistent haemodynamic profile, which may be different from that of other etiologies as the heart has adapted to pressure overload for pulmonary vasoconstriction. Combination of right heart catherization (RHC) and echocardiography at diagnosis and at follow-up allows long-term survival grouping on a haemodynamic basis better than with a peak oxygen uptake. Four cases of chronic obstructive pulmonary disease with pulmonary hypertension (PH) illustrate that recognition of a consistent hemodynamic profile characterized by moderate increase of pulmonary pressures and resistance neglected by the current groupings of PH (group 3 mild/moderate polmonare) may lead to more efficacious management of PH in COPD.

15. Patient Perspectives and Quality of Life

This article is a summary of the presentation of a conference that took place at the World Congress of Cardiology. The aim of the conference was to present the most recent clinical and haemodynamic knowledge on the matter of primary pulmonary hypertension and other pulmonary disorders resulting in pulmonary hypertension, diagnostic approaches and the implementation of the guidelines. A summarised description of the main issues presented during the mentioned conference is discussed in this article.

The sponsor of the conference was a French group. The chairman of the conference was Mr A. Sommier, and the discussant was Professor R. Higenbottam. Three main subjects were discussed during the conference. The first one was an update on clinical and prognostic aspects in which some problem areas concerning the pharmacological approach were pointed out. The second subject concerned the treatment of primary pulmonary hypertension with prostacyclin. A brief historical review of controlled studies that have been reported or which have been presented during the conference was also presented. The third issue discussed was the introduction and discussion of the Guidelines for diagnosis and treatment of the patients with primary pulmonary hypertension. (Ruopp & Cockrill, 2022)(You et al.2022)(Olsson et al.2023)

16. Ethical Considerations in Diagnosis and Treatment

It is not only baker's dozen but also "Search and thou canst find". You will find it in that delightful tale "The Golden Key". '^He was lying on the grass near the house on the hill-top, able to see many layers of stars beyond", Gaiman said, which is a reflection of William Blake's mystical positions "to see a World in a Grain of Sand, And a Heaven in a Wild Flower, Hold Infinity in the palm of your hand, And Eternity in an hour". Pulmonary arterial pressures can be estimated by the velocity of the tricuspid regurgitation using the simplified Bernoulli equation (Peak TR Velocity X 4). However, a right heart catheterization is necessary to establish the diagnosis and to assess the severity of pulmonary hypertension (Olschewski, 2021). Chronic lung diseases and especially chronic obstructive pulmonary diseases (COPD) are strongly associated with pulmonary hypertension. Even mildly elevated pulmonary arterial pressures are associated with an

increased mortality. The pathophysiology of COPD-associated pulmonary hypertension is complex and includes hypoxic pulmonary vasoconstriction but also remodeling of vascular and distal pulmonary arteries through endothelial dysfunction and inflammation. Similar mechanisms as found in severe idiopathic pulmonary arterial hypertension (PAH) exist. However, only a small fraction of patients with COPD suffers from severe pulmonary hypertension. It appears that the vascular remodeling goes to point of no return only at an arterial partial pressure of oxygen below 50 mm Hg; on the other hand, there is also a substantial fraction of patients with mild COPD who develop severe pulmonary hypertension. Not all pulmonary pressure elevations are due to COPD. Left heart diseases like heart failure with preserved ejection fraction or mitral valve stenosis may cause pulmonary hypertension where treatment of the left heart disease may partially reverse the pulmonary hypertension. Also, chronic thromboembolic disease should be excluded as it is partially curable by pulmonary thromboendarterectomy. In addition, there are patients with the pulmonary arterial hypertension COMBO due to his complex developmental diseases - also termed diseases with unrepairable he shunt - who may also encounter COPD or another chronic lung disease as commitment. Pulmonary hypertension (PH) due to chronic lung diseases falls into World Health Organization (WHO) Group 3. Some patients with chronic lung disease are also pulmonary hypertension have severe combined functional impairment and lung parenchymal abnormalities so that severe group Group 1 pulmonary arterial hypertension may remain underdiagnosed. It is important to establish if the Group 1 PAH or Group 1 PAH due to connective tissue disease or HIV may benefit from specific drugs active on the pulmonary arterial vasculature. All these definitions and caveats are part of the current World Symposia on Pulmonary Hypertension (WSPH) task-frost. Two were born in Far Away, High Up There, Beyond The Elevens-Trees, the Roaring Queens and The Mountains of Ice, Except They Were Not Born. King tells Gaiman, and Gaiman tells you (and other ones, and they tell each other). The course of Jeliza-Rose is "miraculous" (not in the wonderful sense of the world, rather in its etymological understanding of an object of sight to be admired) like the stained glass window she wears (part of her found clothes), behind which she hides, "embrace[d]", in a disused church in the same colors: blue and red. The intensification of the spectral qualities of color, or colors' translucence and its dramatization by cinematographic filters, set design, dress, ritual objects, gestures, and light effects create a sense of life in colors, and colors as life. They are where life resides, pulsates, in the movie. "You cannot really be in the world I come from and not know some things about life, and color, and constancy." Queen Valentine tells Shiel in A Fish Dinner in Memison, and Shiel must be told, because all gets lost in the painful exhaustion of the city who looks too much with its besieging, crop-less gaze, and with its vile names of heavy metal-like qualities. (Olsson et al.2023)(Kovacs et al.2022)(Stolz et al.2022)(Zhang et al.2022)

Non-invasive Diagnosis of Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease: Comparison of Information from ECG, Radiological Measurements, Echocardiography, and Myocardial Scintigraphy in Emergency and Pediatric Settings

Pulmonary hypertension (PH) is a severe complication of chronic obstructive pulmonary disease (COPD), characterized by elevated pulmonary artery pressure, leading to increased mortality and morbidity (Zhang et al., 2022). Early diagnosis and intervention are crucial for managing PH in COPD patients, particularly in pediatric and emergency settings where timely diagnosis is essential. Non-invasive diagnostic techniques such as electrocardiography (ECG), radiological measurements, echocardiography, and myocardial scintigraphy have been increasingly employed to assess PH without the need for invasive procedures like right heart catheterization (RHC) (Olsson et al., 2023).

Electrocardiography (ECG) is widely used in clinical practice to evaluate heart rhythm and identify right heart strain, a sign of PH. ECG can indicate right ventricular hypertrophy, a common manifestation of PH. However, while ECG is valuable for identifying signs of heart failure or strain, it cannot directly measure pulmonary artery pressure. Thus, its sensitivity and specificity in diagnosing PH are limited, especially in pediatric patients, where the clinical signs of PH may be more subtle (Zhang et al., 2022).

Radiological Measurements, including chest X-rays and computed tomography (CT) scans, are essential tools for evaluating the structural changes in the lungs and heart associated with PH. CT scans, in particular, can identify pulmonary vascular abnormalities and assess the size of the heart chambers and pulmonary arteries. In emergency settings, CT scans can also detect other potential causes of respiratory distress, such as pulmonary embolism, which can contribute to PH (Gopalan et al., 2017). However, these imaging techniques do not provide direct measurements of pulmonary artery pressure and thus are limited in their ability to definitively diagnose PH.

Echocardiography, often considered the gold standard among non-invasive methods for diagnosing PH, is particularly effective in both emergency and pediatric settings. It provides real-time, bedside measurements of the right ventricular pressures and estimates of pulmonary artery pressures through Doppler ultrasound. This makes echocardiography highly useful in both emergency situations and for ongoing monitoring in pediatric patients with COPD or congenital heart disease (Olsson et al., 2023). Despite its advantages, echocardiography can be affected by factors such as patient body habitus and operator skill, potentially impacting the accuracy of the results.

Myocardial Scintigraphy, a type of nuclear medicine imaging, assesses myocardial perfusion and function, offering valuable insights into the effects of PH on the heart. While it is not commonly used as a first-line diagnostic tool for PH, myocardial scintigraphy can provide important information in complex cases, especially in pediatric patients with underlying heart conditions or those at risk for PH (He et al., 2022). However, the use of myocardial scintigraphy is limited by its availability, cost, and radiation exposure, making it less feasible for routine screening compared to other non-invasive methods.

In **emergency settings**, a combination of these non-invasive techniques can enhance diagnostic accuracy and facilitate timely intervention. ECG and radiological imaging can be used to quickly exclude other conditions, while echocardiography and myocardial scintigraphy provide more specific information regarding the presence of PH and its impact on the heart (Gopalan et al., 2017). In pediatric cases, where the symptoms of PH can overlap with other respiratory or cardiac conditions, a multi-modal approach can help identify PH early, allowing for more effective management and better patient outcomes.

In conclusion, non-invasive diagnostic methods such as ECG, radiological measurements, echocardiography, and myocardial scintigraphy are essential tools for diagnosing PH in patients with COPD, particularly in emergency and pediatric settings. While each method has its limitations, their combined use can significantly improve the accuracy and timeliness of PH diagnosis, ultimately enhancing patient management and outcomes. Further research into the development of more advanced, cost-effective non-invasive diagnostic tools for PH will be essential for improving early diagnosis, especially in resource-limited settings where invasive procedures are not always feasible.

17. Conclusion

Exercise tolerance in patients with COPD is reduced due to ventilatory limitation, gas exchange abnormalities, and deconditioning. Pulmonary hypertension is a common complication in COPD associated with increased mortality. COPD patients usually terminate physical activity when the ventilatory requirement exceeds their maximal ventilatory capacity. Impaired exercise tolerance in COPD patients suggests that cardiopulmonary exercise test is a valuable tool to reveal whether they have pulmonary hypertension or not. However, the results from previous studies are diverging, making it difficult to separate COPD patients with and without pulmonary hypertension based on the cardiopulmonary exercise test variables. Different outcomes are partially explained by differences in study populations, exercise protocols, or methods for diagnosing pulmonary hypertension. In evaluating pulmonary hypertension in COPD patients, it is relevant to consider left heart function, as arterial hypertension and left ventricle diastolic dysfunction are frequent in COPD.

Most previous studies are retrospective. There are few prospective studies of nonselected COPD populations with pulmonary hypertension presenting cardiopulmonary exercise test results, which gives a rationale for this study where we included COPD outpatients with varying degrees of airway obstruction. The aim of this study was to evaluate the entire course of exercise during cardiopulmonary exercise test in COPD outpatients. This includes onset of exercise, peak exercise, and recovery, the latter including assessment time points at 1, 3, 6, and 9 min after the termination of exercise since these are sequentially used to highlight different subnormal cardiorespiratory responses to exercise. A further aim was to assess whether the variables obtained during cardiopulmonary exercise test correlate with echocardiographic assessment of pulmonary hypertension. In this study, none of the cardiopulmonary exercise test variables were found to predict concomitant pulmonary hypertension found at echocardiography, or to reflect different responses to exercise in COPD patients with pulmonary hypertension compared to COPD patients without pulmonary hypertension. This illustrates

the complexity in evaluating pulmonary hypertension in COPD patients using cardiopulmonary exercise test and highlights the need for additional assessment tools.

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