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Pulmonary Arterial Hypertension (PAH)

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Pulmonary Arterial Hypertension (PAH)

- PAH is a progressive disease caused by narrowing or tightening (constriction) of the pulmonary arteries, which connect the right side of the heart to the lungs
- As PAH develops, blood flow through the pulmonary arteries is restricted and the right side of the heart becomes enlarged due to the increased strain of pumping blood through the lungs

Pulmonary Arterial Hypertension (PAH)

- Although symptoms of PAH are non-specific, it is this strain on the heart and lack of blood to the lungs that leads to the common symptoms of PAH, such as breathlessness, fatigue, weakness, angina, syncope, and abdominal distension

Pulmonary Arterial Hypertension (PAH)

- By definition, PAH is characterised by
  - an increase in mean pulmonary arterial pressure (PAP) to at least 25 mmHg at rest
  - a mean pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg

Changes in the Pulmonary Arteries in PAH

- The increase in pulmonary vascular resistance observed in patients with PAH is related to a number of progressive changes in the pulmonary arterioles, including:
  - vasoconstriction
  - obstructive remodelling of the pulmonary blood vessel walls due to cell proliferation within the various layers of the vessel wall (smooth muscle cell and endothelial cell proliferation)

Changes in the Pulmonary Arteries in PAH

- The increase in pulmonary vascular resistance observed in patients with PAH is related to a number of progressive changes in the pulmonary arterioles, including:
  - inflammation
  - in situ thrombosis

Changes in the Pulmonary Arteries in PAH

- The most prominent histological feature of PAH is a thickening of the three cellular layers (the intima, media, and adventitia) that line the blood vessels, which is due to a process of cell enlargement termed hypertrophy
- Other changes include development of plexiform lesions (focal proliferations of endothelial and smooth muscle cells that are a classic characteristic of PAH), and in situ thromboses

Changes in the Pulmonary Arteries in PAH

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PAH Represents Group 1 within the Pulmonary Hypertension World Health Organization (WHO) Clinical Classification System

PAH Group 1

- Idiopathic (IPAH)
- Heritable (HPAH)
  - bone morphogenetic protein receptor type 2 (BMPR2)
  - activin receptor-like kinase 1 gene (ALK1), endoglin (with or without haemorrhagic telangiectasia)
  - unknown

PAH Group 1

- Drug- and toxin-induced
- Associated with (APAH):
  - connective tissue diseases
  - human immunodeficiency virus (HIV) infection
  - portal hypertension

PAH Group 1

- Drug- and toxin-induced
- Associated with (APAH):
  - congenital heart disease (CHD)
  - schistosomiasis
  - chronic hemolytic anemia

PAH Group 1

- Persistent pulmonary hypertension of the newborn (PPHN)

Classification of PAH

- Idiopathic PAH (IPAH)
  - one of the more common forms of PAH, which corresponds to sporadic disease in which there is neither a family history of PAH nor an identified risk factor

Classification of PAH

- Heritable PAH (HPAH)
  - accounts for at least 6% of cases of PAH
  - mutations in the bone morphogenetic protein receptor 2 (BMPR2) have been identified in the majority of cases
- Drug and toxin-induced
  - PAH is also a rare side effect of certain anorexigenic agents, such as fenfluramine (incidence is decreasing as it is no longer available)

PAH can be associated with a number of conditions (associated PAH [APAH]), which accounts for most cases.

PAH Can Be Associated With a Number of Conditions

- PAH associated with connective tissue disease:
  well-recognized complication of connective tissue diseases, such as systemic sclerosis (SSc or scleroderma) and systemic lupus erythematosus (SLE)

PAH Can Be Associated With a Number of Conditions

- PAH associated with HIV infection
  is relatively well-documented, complication of HIV infection
- Highly active anti-retroviral therapy (HAART) has markedly improved survival rates in HIV patients, and so long-term conditions such as pulmonary arterial hypertension are increasingly responsible for HIV-associated morbidity and poor prognosis

PAH Can Be Associated With a Number of Conditions

- PAH associated with portal hypertension
- PAH is a well-recognized complication of chronic liver diseases that develop as a result of portal hypertension (also called portopulmonary hypertension) and makes up around 10% of the PAH population

PAH Can Be Associated With a Number of Conditions

- PAH associated with schistosomiasis
- Schistosomiasis is a parasitic disease caused by trematode flatworms of the genus schistosoma
  - patients with schistosomiasis and PAH can have the required specific clinical and pathological characteristics to be included in the APAH group
  - the prevalence of PAH in patients with schistosomiasis is around 4.6%

PAH Can Be Associated With a Number of Conditions

- PAH associated with sickle cell disease - the prevalence of PAH in patients with sickle cell disease is around 2–3.75%
- PAH associated with congenital heart disease - congenital heart disease (CHD) is relatively common and affects around 1% of the population
- Approximately 5–10% of adults with CHD will go on to develop PAH

PAH Can Be Associated With a Number of Conditions

- The most severe form is Eisenmenger's syndrome, which is associated with the reversal of an initial left-to-right shunt to a right-to-left shunt causing cyanosis and limited exercise capacity
- Patients with PAH associated with CHD also include those with mild to moderate systemic-to-pulmonary shunts with no cyanosis at rest, patients with small defects, and those with residual PAH following corrective cardiac surgery

Incidence of Pulmonary Arterial Hypertension

- Although PAH is a rare disease, with an estimated prevalence of 15–50 cases per million, the prevalence of PAH in certain at-risk groups is substantially higher

How common is PAH?

- PAH is rare - there is an estimated prevalence of 15–50 cases per million
- Idiopathic PAH (IPAH) has an annual incidence of 1–2 cases per million people in the U.S. and Europe
- 2-4 times as common in women as men

How common is PAH?

- Prevalence is higher in at-risk groups:
  - systemic sclerosis (~7–12%)
  - HIV infection (0.5%)
  - sickle cell disease (2–3.75%)
  - schistosomiasis (4.6%)

Etiology of Pulmonary Artery Hypertension

- The exact causes of the development of PAH remain unknown
- However, research has led to a better understanding of underlying pathological mechanisms
- PAH is recognized as a complex, multi-factorial condition involving numerous biochemical pathways and different cell types

Etiology of Pulmonary Artery Hypertension

- Endothelial dysfunction, an abnormality of the inner lining of blood vessels, is believed to occur early in disease pathogenesis, and this leads to endothelial and smooth muscle cell proliferation followed by structural changes (remodelling) of the pulmonary vascular bed, which in turn results in an increase in pulmonary vascular resistance

Etiology of Pulmonary Artery Hypertension

- Vascular remodelling itself involves every layer of the vessel wall and is characterised by proliferative and obstructive changes involving many cell types; including endothelial cells, smooth muscle cells, and fibroblasts

Etiology of Pulmonary Artery Hypertension

- Inflammatory cells and platelets may also play a significant role in PAH

Etiology of Pulmonary Artery Hypertension

- Endothelial dysfunction results in chronically impaired production of vasodilatory mediators, such as nitric oxide (NO) and prostacyclin, along with prolonged overexpression of vasoconstrictors, such as endothelin-1 (ET-1), which not only affect vascular tone but also promote vascular remodelling
- These substances are important therapeutic targets for new treatment options in PAH

The Role of Endothelin

- Endothelin-1 (ET-1) is produced by endothelial cells lining the blood vessels (high levels of endothelin are seen in patients with PAH due to various etiologies and correlate with disease severity, resulting in a number of detrimental effects, primarily in the vasculature):
  - fibrosis
  - hypertrophy and proliferation of cells, which can lead to thickening, narrowing, and occlusion of blood vessels

The Role of Endothelin

- Endothelin-1 (ET-1) is produced by endothelial cells lining the blood vessels (high levels of endothelin are seen in patients with PAH due to various etiologies and correlate with disease severity, resulting in a number of detrimental effects, primarily in the vasculature):
  - inflammation
  - vasoconstriction

The Role of Endothelin

- Endothelin binds to two receptors, known as ET_A and ET_B
- Both receptors are implicated in PAH and mediate the deleterious effects of endothelin
- Endothelin receptor antagonism can either mitigate the effects of only one (single ET_A antagonist) or both (dual ET_A and ET_B receptor antagonist) receptor types

The Role of Endothelin

- Therapy with orally administered endothelin receptor antagonists (ERAs) that block the binding of endothelin to one or both receptors aims to mitigate the deleterious effects of the high levels of endothelin seen in PAH

The Role of Prostacyclin

- Prostacyclin is a potent vasodilator as well as an inhibitor of platelet activation
- Patients with PAH have low levels of prostacyclin, which promotes vasoconstriction in the pulmonary vasculature and a tendency for smooth muscle cell proliferation and platelet activation
- This may also encourage the formation of thrombi, which have been found in both the small distal and the proximal elastic pulmonary arteries

Administering Prostacyclin

- Therapy with prostacyclin or prostacyclin analogues can help to correct this deficiency
  - although administering this form of treatment may be complex due to the fact that some prostacyclins are broken down rapidly within the body
  - in most cases these substances need to be given as a continuous intravenous

Administering Prostacyclin

- Therapy with prostacyclin or prostacyclin analogues can help to correct this deficiency
  - subcutaneous infusion
  - by inhalation

Pulmonary Arterial Hypertension: Symptoms

The Role of Nitric Oxide

- Nitric oxide
  - potent vasodilator
  - possesses anti-proliferative properties
  - production of nitric oxide is impaired in PAH
  - vasodilatory effect is mediated by cGMP
  - rapidly degraded by phosphodiesterases (PDEs)
  - therapy with oral PDE-5 inhibitors reduces degradation

Etiology of Symptoms of PAH

- Changes to the pulmonary vasculature lead to the typical symptoms of PAH
- The symptoms are caused by the high resistance to blood flow through the lungs, which results in increased stress on the heart
- This can severely impact a patient's ability to exercise or carry out normal daily activities

What are the symptoms of PAH?

- Common early symptoms include:
  - breathlessness (dyspnea), particularly during physical activity
  - fatigue
  - dizziness

What are the symptoms of PAH?

- Common early symptoms include:
  - syncope, also on physical activity (rare)
  - peripheral edema
  - chest pain, again particularly during physical activity

Symptoms of PAH

- The symptoms of PAH may not be obvious at first and are often attributed to more common conditions
- Over time, however, they can become more severe and begin to limit normal activities
- As the disease progresses, some patients may experience constant dyspnea and fatigue so that even simple tasks, such as getting dressed and walking short distances, become difficult

Symptoms of PAH

- As the early symptoms of PAH are often mild, time from symptom onset to disease diagnosis is, on average, more than 2 years
- This means that PAH is frequently not recognized until the disease is relatively advanced

Diagnosing PAH

How is PAH Diagnosed?

- PAH is a challenging disease to diagnose accurately; diagnosis cannot be made on symptoms alone
- Requires invasive investigations and significant experience to manage patients effectively
- As such, current guidelines recommend that the diagnosis and management of PAH is coordinated by expert centers (dependent on regional variations)

How is PAH Diagnosed?

- The non-specific nature of symptoms associated with PAH means that the diagnosis cannot be made on symptoms alone
- Once a suspicion of PAH has been raised, the aim is to:
  - confirm or exclude the diagnosis of pulmonary hypertension (PH) and, if present, establish its etiology, assess disease severity, as well as decide on subsequent management and treatment strategies

How is PAH Diagnosed?

- The diagnosis of PAH involves a series of investigations to determine:
  - whether there is a likelihood of PAH being present
  - confirm the diagnosis based on initial non-invasive testing
  - clarify the specific etiology

How is PAH Diagnosed?

- The diagnosis of PAH involves a series of investigations to determine:
  - evaluate the functional and hemodynamic impairment of the individual patient
  - determine an appropriate treatment category

Diagnostic Steps Formalized into Clinical Practice Guidelines for the Diagnosis of PAH, both in Europe and the U.S.

European Society of Cardiology/European Respiratory Society (ESC/ERS) Clinical Guidelines for the Diagnosis of PAH

and

American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Diagnostic Approach to PAH

Four-Stage Approach to Diagnosis of PAH

1. Clinical suspicion of PAH
   - symptoms
   - known risk factors
2. Exclusion of Group 2 (left heart disease) and Group 3 (lung disease) pulmonary hypertension (PH) electrocardiogram (ECG), chest radiograph, echocardiography, pulmonary function tests (PFTs), high-resolution computed tomography (HRCT)

Four-Stage Approach to Diagnosis of PAH

3. Exclusion of Group 4 chronic thromboembolic pulmonary hypertension (CTEPH) - (CTEPH) PH - ventilation/perfusion lung scan
4. PAH evaluation and characterization
   - CT pulmonary angiography, cardiac MRI, hematology, biochemistry, serology, and ultrasonography
   - functional class and exercise capacity
   - right heart catheterization (RHC)

Four-Stage Approach to Diagnosis of PAH

1. Clinical suspicion of PAH
   - symptoms such as exertional dyspnea, syncope, angina, and/or progressive limitation of exercise capacity without apparent risk factors, symptoms, or signs of common cardiovascular and respiratory disorders
   - patients with associated conditions and/or risk factors (e.g., family history, connective tissue diseases, HIV)

Four-Stage Approach to Diagnosis of PAH

2. Exclusion of Group 2 (left heart disease) and Group 3 (lung disease) PH:
   - clinical history
   - electrocardiogram (ECG)
   - chest radiograph (X-ray)

   …are requested in order to identify the presence of Group 2 (left heart disease) or Group 3 (lung diseases)

Four-Stage Approach to Diagnosis of PAH

2. Exclusion of Group 2 (left heart disease) and Group 3 (lung disease) PH:
   - transthoracic echocardiogram
   - pulmonary function tests (PFTs)
   - high-resolution computed tomography (HRCT) of the chest

   …are requested in order to identify the presence of Group 2 (left heart disease) or Group 3 (lung diseases)

Four-Stage Approach to Diagnosis of PAH

3. Exclusion of Group 4 PH
   - if PH Groups 2 or 3 are not found, less common causes of PH should be sought
   - Example: ventilation/perfusion lung scan is used to exclude Group 4 chronic thromboembolic pulmonary hypertension (CTEPH)

Four-Stage Approach to Diagnosis of PAH

4. PAH evaluation and characterization
   - a range of other tests can be performed to refine the final diagnosis, including CT pulmonary angiography, cardiac magnetic resonance imaging (CMRI), hematology, biochemistry, immunology, serology, and ultrasonography

Four-Stage Approach to Diagnosis of PAH

4. PAH evaluation and characterization
   - the degree of limitation to the patient caused by PAH is assessed by determining functional class and by exercise tests such as the six-minute walk test (6MWT)
   - however, the diagnostic gold standard for the confirmation of a diagnosis of PAH is right heart catheterization (RHC)

Echocardiography – Value as a Screening Tool

- Doppler transthoracic echocardiography (TTE) can be used as a non-invasive screening test for pulmonary hypertension
- Pulmonary arterial pressure (PAP) can be estimated from the tricuspid regurgitant (TR) jet measured by TTE and a range of other measures can be obtained, which provide information about the cause and consequences of PH

Right Heart Catheterization – Diagnostic Gold Standard

- Right heart catheterization (RHC) is required for a definitive diagnosis of PAH to assess the severity of hemodynamic impairment, and to test the vasoreactivity of the pulmonary circulation
- PAH is defined as a sustained elevation of mean pulmonary arterial pressure (mPAP) to ≥25 mmHg at rest, and a mean pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg

Right Heart Catheterization Hemodynamic Assessment

- The catheter is placed in the heart during RHC to record standard hemodynamic measurements such as right atrial pressure (RAP), pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP)

Screening Patients for PAH

Screening for PAH

- European and U.S. guidelines now recognize that early diagnosis and therapeutic intervention may offer an improved outlook for patients with PAH
  - European and U.S. guidelines recommend annual screening with Doppler echocardiography, which is currently the most effective method for screening
  - right heart catheterization needs to be performed for a definitive diagnosis of PAH

Screening for PAH

- One method of improving early diagnosis is the introduction of screening programs for high-risk patient populations

- These programs screen patients for the presence of PAH while they are not showing obvious symptoms

Screening for PAH

- High-risk patient populations are those patients with conditions known to be associated with a high risk of developing PAH, including:
  - family members of a patient with heritable PAH (HPAH)
  - patients with systemic sclerosis (SSc [scleroderma])
  - patients with HIV
  - patients with portopulmonary hypertension (PoPH)
  - patients with congenital heart disease

Value of Screening for PAH

- In the U.S., over 60% of newly diagnosed patients with PAH enrolled in the REVEAL registry were in functional class III
  - however, PAH was detected at an earlier stage during a national screening program in a high-risk population, demonstrating the potential value of a screening strategy

Value of Screening for PAH

- Results of a PAH registry in France
  - showed that without screening the majority of patients were diagnosed in WHO functional capacity (FC) of III or IV, and only 24% of patients were in the less severe WHO FC II
  - with screening, PAH was detected at an earlier stage

Pulmonary Arterial Hypertension Treatment

How is PAH Treated?

- Management is complex, involving use of a range of treatment options which can be broadly broken down into four main categories:
  - general measures
  - conventional or supportive therapy
  - advanced therapy (PAH-specific therapy)
  - surgical intervention

How is PAH Treated?

- While there is currently no cure for the disease, modern advanced PAH therapies can:
  - markedly improve a patient's symptoms
  - slow the rate of clinical deterioration

General Measures

- General measures
  - aim to limit any potentially deleterious effects of the patient's external circumstances on their PAH disease, and include:
    - avoid pregnancy
    - prevention and prompt treatment of chest infections
    - awareness of the potential effects of altitude

Conventional or Supportive Therapy

- Conventional or supportive therapy
  - aims to provide symptomatic benefit, measures include:
    - supplemental oxygen
    - oral anticoagulants
    - diuretics
    - calcium channel blockers

Advanced Therapy (‘PAH-specific therapy’)

- PAH-specific therapies have been developed to target one of three major pathways known to be involved in the development of PAH and have, to varying degrees, been shown to affect the disease process:
  - endothelin receptor antagonists (ERAs)
  - synthetic prostacyclin and prostacyclin analogues
  - phosphodiesterase-5 (PDE-5) inhibitors

Advanced (PAH-Specific) Therapy Endothelin Receptor Antagonists (ERAs)

- Endothelin receptor antagonists (ERAs)
  - oral treatments that act by blocking the binding of endothelin, which is implicated in the pathogenesis of PAH through its actions on the pulmonary vasculature to either one (single antagonist) or both (dual antagonist) of its receptors

Advanced (PAH-Specific) Therapy Endothelin Receptor Antagonists (ERAs)

- Endothelin receptor antagonists (ERAs)
  - clinical trials have shown that treatment with ERAs has a beneficial effect on exercise capacity, WHO Functional Class (FC), hemodynamics and time to clinical worsening in patients with PAH

Advanced (PAH-Specific) Therapy Synthetic Prostacyclin and Prostacyclin Analogues

- Synthetic prostacyclin and prostacyclin analogues
  - act by helping to correct the deficiency of endogenous prostacyclin seen in patients with PAH
  - the clinical use of prostacyclin in patients with PAH has been extended by the synthesis of more stable analogues for intravenous infusion, as well as those that can be given by subcutaneous infusion, or by inhalation

Advanced (PAH-Specific) Therapy Phosphodiesterase-5 (PDE-5) Inhibitors

- Phosphodiesterase-5 (PDE-5) inhibitors
  - oral agents which act on the nitric oxide (NO) pathway to induce vasodilation and also have antiproliferative effects on vascular smooth muscle cells
  - clinical trials have shown that treatment with PDE-5 inhibitors has a beneficial effect on exercise capacity, hemodynamic parameters, and symptoms in patients with PAH

Surgical Intervention

- For patients with severe PAH who do not respond to treatment with advanced therapies, surgery may be the only option
- Surgical options include:
  - balloon atrial septostomy, which creates a small hole between the right and left atria to reduce the pressure and therefore the stress on the right heart
  - lung or heart and lung transplantation

Treatment Guidelines: Goal-Oriented Therapy

Treatment Guidelines: Goal-Oriented Therapy

- Treatment guidelines recommend that patients with PAH receive initial monotherapy
- Once treatment is initiated, patients should be monitored regularly and their response to therapy assessed using a range of clinical, exercise, hemodynamic, and echocardiographic parameters

Treatment Guidelines: Goal-Oriented Therapy

- Treatment guidelines recommend that, if the patient shows an inadequate clinical response to monotherapy, combination therapy using a combination of PAH-specific therapies from different classes (e.g., prostanoids, endothelial receptor antagonists, phosphodiesterase-5 inhibitors) should be considered

Treatment Guidelines: Goal-Oriented Therapy

- Predetermined goals based on parameters that have been shown to be associated with better prognosis should be set for the patient, and regular follow-up visits are recommended in order to ascertain progress towards the treatment goals

Treatment Guidelines: Goal-Oriented Therapy

- Patient condition can be categorized as:
  - stable and satisfactory: a patient fulfilling the majority of goals or targets
  - stable but not satisfactory: a patient who, although stable, has not achieved the status that the patient and treating physician would consider desirable and some of the treatment goals have not been met

Treatment Guidelines: Goal-Oriented Therapy

- Patient condition can be categorized as:
  - unstable and deteriorating: a patient not meeting goals or targets, and exhibiting a number of parameters associated with a worse prognosis
  - ‘stable but not satisfactory’ or ‘unstable and deteriorating’: re-evaluation and consideration for escalation of treatment

The Importance of Early Identification and Intervention in PAH

The Importance of Early Identification and Intervention in PAH

- Early diagnosis and therapeutic intervention may offer an improved outlook for patients
- Prognosis and response to treatment have both shown to be better for patients with less severe disease (e.g., WHO Functional Class I/II) compared with those who do not begin targeted therapy until their PAH has reached a more severe stage (e.g., WHO FC III/IV)

The Importance of Early Identification and Intervention in PAH

- Early diagnosis poses a challenge to healthcare professionals because many of the initial symptoms of PAH are mild and non-specific
- Many patients are not diagnosed until the disease is already quite severe

Assessing the Patient

Assessing the Severity of PAH

- Assessing patients with pulmonary arterial hypertension (PAH) involves evaluating the severity of their disease using a range of:
  - clinical assessment
  - exercise tests
  - biochemical markers
  - echocardiographic assessment
  - hemodynamic assessments

Assessing the Severity of PAH

- The clinical assessment of the patient has a pivotal role in the choice of the initial treatment, the evaluation of the response to therapy, and the possible escalation of therapy if needed
- A number of parameters have been proven to have prognostic significance in PAH, although their value in a given patient may vary depending on the underlying etiology of the disease

Functional Classification of PAH Disease

Functional Classification of PAH Disease

- The clinical severity of PAH is classified according to a system originally developed for heart failure by the New York Heart Association (NYHA) and then modified by the World Health Organization (WHO) for patients with PAH

Functional Classification of PAH Disease

- This system grades PAH severity according to the functional status of the patient, linking symptoms with activity limitations, and allows clinicians to quickly and accurately predict disease progression and prognosis, as well as the need for specific treatment regimens, irrespective of the underlying etiology of PAH

Functional Classification of PAH Disease

Functional Class	Symptomatic Profile
I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause dyspnea or fatigue, chest pain, or near syncope.
II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Adapted from guidelines for the diagnosis and treatment of pulmonary hypertension[1]

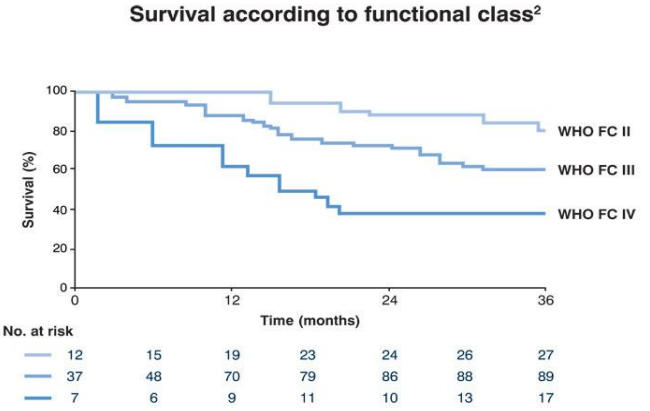
Functional Class and Survival

Functional Class and Survival

- WHO FC is a powerful predictor of survival in patients with PAH
  - in a recent French study, lower functional class (I/II) was found to be positively and significantly associated with survival (Figure)

Functional Class and Survival

Even with advanced medical therapy, patients in WHO FC IV continue to have extremely poor survival rates



Functional Class and Survival

- Data from the U.S. REVEAL registry showed that functional class IV was independently associated with increased mortality
- Given this link with prognosis, improvement from WHO FC III/IV to WHO FC II and improvement or maintenance of patients with early signs at WHO FC I/II are very important goals of therapy

Six-Minute Walk Test (6MWT)

Six-Minute Walk Test (6MWT)

- The six-minute walk test (6MWT) is a key test in PAH management because it is a measure of the patient's functional limitation and correlates with peak aerobic capacity
- It is also a simple test to perform, which is inexpensive and convenient

Six-Minute Walk Test (6MWT)

- In addition to distance walked, dyspnea on exertion, and O_2 saturation can also be recorded, which can provide further information regarding the patient's condition

Six-Minute Walk Test (6MWT)

- Results of the 6MWT have been shown to correlate with functional class and the distance walked significantly decreases in proportion to the severity of NYHA FC.

Six-Minute Walk Test (6MWT)

- It should be noted that, despite these advantages, the 6MWT is only properly validated for patients with IPAH
- It is not yet clear whether it is appropriate for the assessment of treatment success in patients with, for example, PAH-SSc (scleroderma) where accompanying conditions can make the 6MWT difficult

Six-Minute Walk Test (6MWT)

- It also has not been standardized for all populations, and it is important that the test is performed under supervision according to a standardized protocol in order to allow meaningful comparisons

Cardiopulmonary Exercise Testing

Cardiopulmonary Exercise Testing

- Cardiopulmonary exercise testing (CPET) assesses lung gas exchange and gives a more sensitive and comprehensive measure of exercise capacity than the 6MWT

Cardiopulmonary Exercise Testing

- It is a maximal stress test - the patient exercises at a workload that progressively increases to their symptom tolerance (e.g., the maximum workload the patient can tolerate)
- As such, it is difficult to perform in patients with severe disease

Cardiopulmonary Exercise Testing

- One important measure assessed using CPET is peak O_2 consumption (VO_2 max), which is a measure of the ability of the cardiovascular system to transport oxygen to the tissues and the ability of the cells to use oxygen:
  - it has become the gold standard for assessing a patient's exercise capacity and maximal cardiovascular response
  - PAH patients show reduced peak VO_2 and this measurement correlates with a patient's prognosis

Cardiopulmonary Exercise Testing

- Despite offering some advantages over the 6MWT in terms of sensitivity, these tests are more difficult to perform and require specialist equipment
- As they are a maximal stress test, they are not suitable for more severely affected patients who may not be able to tolerate the exercise and may be exposed to risk of syncope and discomfort

Hemodynamic Parameters

- Measured by right heart catheterization (RHC)
- Important diagnostic and prognostic markers in the assessment of PAH
- Correlate with clinical status, WHO FC, exercise capacity, and prognosis
- Also used to assess treatment effect

Hemodynamic Parameters

- Prognosis is significantly correlated with markers of right ventricular function, including mean right atrial pressure (mRAP) and mean cardiac index (CI)
- Normalization of hemodynamics may therefore be considered a suitable goal or treatment measure

Biochemical Markers

- Serum levels of a protein known as N-terminal prohormone brain-type natriuretic peptide (NT-proBNP) have been shown to be associated with prognosis in PAH

Biochemical Markers

- A level of serum NT-proBNP below 1400 pg/mL seems to identify patients with good prognosis and who are unlikely to need escalation of treatment in the immediate future
- However, cut-off levels still need to be verified in controlled trials, and our understanding of the role of this marker is still emerging

PAH-SSc (Scleroderma) Explained

PAH in Patients with SSc (PAH-SSc)

- Around 15% of all cases of pulmonary arterial hypertension (PAH) in a recent French PAH registry and 25% in a U.S. PAH registry were associated with connective tissue disease, and particularly with SSc (scleroderma)
- Patients with SSc (scleroderma) who develop PAH have poorer prognosis than those who do not

PAH in Patients with Scleroderma (PAH-SSc)

- PAH has become one of the leading causes of mortality in SSc (scleroderma) patients, accounting for more than 25% of all SSc-related deaths
- Given the significant incidence of PAH in patients with SSc (scleroderma) and the high mortality associated with this complication if untreated, there is a clear need for early detection and timely treatment before patients show marked clinical and hemodynamic deterioration

How is PAH-SSc (Scleroderma) Detected?

- The diagnosis of PAH in patients with SSc can be particularly challenging, especially in early stages
- SSc affects a number of organs, including the lungs, and can be associated with symptoms such as fatigue and dyspnea, which are also symptoms of PAH
- As a result, detection of PAH in SSc is often delayed and patients are only diagnosed when they have advanced disease with severe clinical and hemodynamic impairment

How is PAH-SSc (Scleroderma) Detected?

- Screening for PAH in SSc is associated with improved outcomes
- However, given the known high incidence of PAH in SSc, echocardiography screening is recommended in all symptomatic patients and screening by echocardiography may also be considered in all SSc patients according to the treatment guidelines

How is PAH-SSc (Scleroderma) Detected?

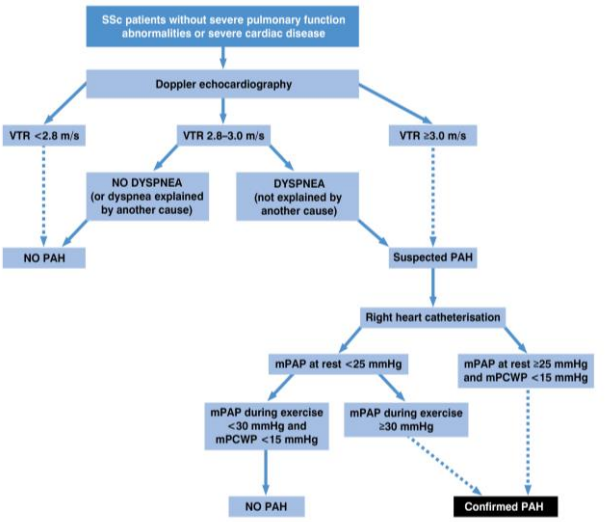
- Recent studies have also shown that screening for PAH in asymptomatic SSc patients is associated with improved outcomes

Screening for PAH in SSc: Suggested screening protocol for the detection of PAH in SSc (scleroderma) patients

Peak velocity of tricuspid regurgitation (VTR)

Mean pulmonary pressure (MPAP)

Mean pulmonary capillary wedge pressure(MPCWP)



Screening for PAH in SSc: Suggested Screening Protocol for the Detection of PAH in SSc Patients

Example screening algorithm:

it is recommended that patients with SSc are regularly assessed using Doppler echocardiography

Screening for PAH in SSc: Suggested Screening Protocol for the Detection of PAH in SSc Patients

The parameter assessed is peak velocity of tricuspid regurgitation (VTR); patients with low VTR (<2.8 m/s) do not have PAH, whereas a high (>3.0 m/s) VTR, or moderate VTR (2.8–3.0 m/s) together with dyspnea, raises the suspicion of PAH

To confirm the diagnosis, patients must then undergo right heart catheterization (RHC)

Treatment PAH-SSc (Scleroderma)

- Available therapies may improve quality of life and exercise capacity, and slow disease progression
- Treatment and reassessment of PAH-SSc (scleroderma) largely the same as for IPAH

Treatment PAH-SSc (Scleroderma)

- Some special consideration required:
  - complications of SSc (scleroderma) may affect ability to perform exercise tests (e.g., 6MWT)
  - potential need to manage multiple complications (e.g., renal, skin, gastrointestinal)
- Referral to expert centers recommended

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Routine Blood Tests for Pulmonary Hypertension Patients

Routine Blood Tests for Pulmonary Hypertension

- There are several blood tests that may be performed routinely on pulmonary arterial hypertension patients
- While none of these blood tests specifically diagnose pulmonary hypertension they are very useful in managing the disease
- We will discuss some of the routine blood tests performed

BNP: B-type Natriuretic Peptide

- A BNP is used to look for heart failure
- If the levels are elevated in the blood, the heart is under strain and failing
- This is useful in pulmonary hypertension patients as it may confirm that the pulmonary artery pressures, and therefore right heart failure, are being controlled by the current therapies a patient is on

BNP: B-type Natriuretic Peptide

- It may reveal that the right heart is stressed due to elevated pressures in the pulmonary arteries and excess fluid in the body
- If the level is elevated, changes may be made to medications or additional tests such as an echocardiogram may be ordered

BMP: Basic Metabolic Panel

- A BMP measures basic electrolytes and basic kidney function and includes glucose, calcium, sodium, potassium, chloride, CO_2, bicarbonate, BUN (blood urea nitrogen), and creatinine
- Many PAH patients are on diuretics, which can lead to wasting of important electrolytes or to renal damage

BMP: Basic Metabolic Panel

- This test is usually done at the first visit and periodically over the course of treatment
- It is a very useful test to perform after making changes to diuretic doses, as it will allow the physician to see if the patient's body is tolerating the medication

CMP: Complete Metabolic Panel

- CMP is a BMP plus albumin, total protein, ALP (alkaline phosphatase), ALT (alanine amino transferase) AST (aspartate amino transferase), and bilirubin
- This test is useful for the same reason a BMP is, plus the added benefit of measuring liver function

CMP: Complete Metabolic Panel

- The increased pulmonary pressure leading to right sided heart failure leads to hepatic congestion, which can cause damage to the organ
- Some endothelin receptor antagonists (ERAs) have been shown to have a low risk of liver damage, thus it is important to check monthly liver function tests

LFTs: Liver Function Tests

- Liver function tests monitors for liver inflammation and damage
- The panel includes ALT (alanine aminotransferase), ALP (alkaline phosphatase), AST (aspartate aminotransferase), bilirubin, albumin, and total protein

LFTs: Liver Function Tests

- With hepatic congestion and some endothelin receptor antagonists (ERAs) having a low risk of liver damage, it is important to check monthly liver function tests
- The LFT panel offers more complete information on the liver and how well it is functioning than a CMP

CBC: Complete Blood Count (Panel of Tests)

- White blood cell count (WBC)
- Red blood cell count (RBC)
- Hemoglobin
- Hematocrit
- Platelet count
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Red cell distribution width (RDW)

CBC: Complete Blood Count (Panel of Tests)

- A CBC can help detect infection, anemia, and other specific hematological abnormalities

CBC: Complete Blood Count (Panel of Tests)

- Pulmonary hypertension patients are on different types of drugs that effect different levels in the CBC
  - some endothelin receptor antagonists (ERAs) can lower a patient's hematocrit
  - immunosuppressants can lower the white blood cell count
  - some prostacyclins lower platelet counts

CBC: Complete Blood Count (Panel of Tests)

- This test is usually performed during or shortly after the first visit and at routine intervals throughout treatment

TSH: Thyroid Stimulating Hormone

- The TSH test is often the test of choice for evaluating thyroid function and/or symptoms of hyperthyroidism or hypothyroidism
- There is thought to be an association between pulmonary arterial hypertension (PAH) and thyroid disease, although it is not well understood
- Most thyroid disorders are easily treated so it is important to diagnose them

Human Chorionic Gonadotropin

- HCG blood pregnancy test that can also be measured in urine
- The qualitative test gives a simple positive (pregnant) or negative (not pregnant) result
- The quantitative test is more in-depth and gives a numerical result that can estimate how far along a pregnancy is

Human Chorionic Gonadotropin

- Pulmonary hypertension patients should not become pregnant, as their hearts do very poorly with the increased blood volume associated in pregnancy
- Certain drugs such endothelin receptor antagonists (ERAs) are known to be teratogenic (cause birth defects), so pregnancy must be avoided and monthly pregnancy tests are required while taking this class of medication

Pulmonary Hypertension Reviewed

- A progressive, life-threatening disorder of the pulmonary circulation characterized by high pulmonary artery pressures, leading to right ventricular failure

Primary Pulmonary Hypertension

- Associated with autoimmune diseases
- Mostly effects women in childbearing years
- Believed to be caused by endothelial dysfunction that leads to remodeling of the pulmonary artery

Secondary Pulmonary Hypertension (Due to Chronic Disorders

- Pulmonary fibrosis/sarcoidosis
- Collagen vascular disease
- Liver disease
- Portal hypertension
- Diet supplements
- Sleep apnea
- HIV

Signs and Symptoms

- Dyspnea
- Weakness/fatigue
- Recurrent syncope
- Signs of right heart failure
- Tricuspid murmur
- Jugular vein distension, pulsation
- Increased pulmonary pressures

Thank You

Pulmonary Arterial Hypertension (PAH)

Jamie K. Roney-Hernandez, DNP, BSHCM, RN-BC, CCRN-K

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