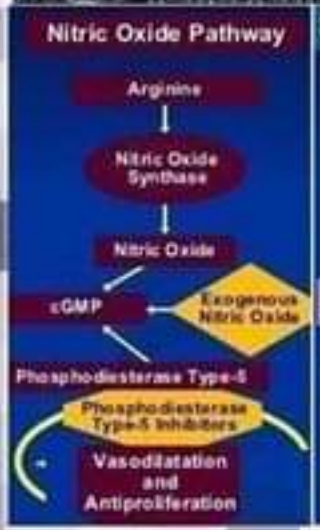
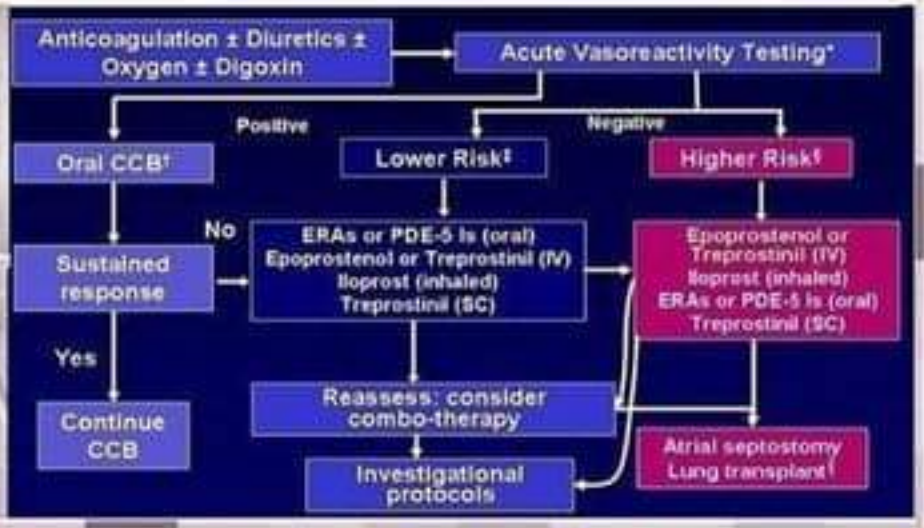
Dr.Amr Shamy

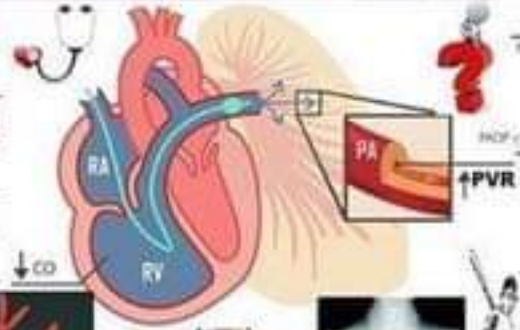
Pulmonary Hypertension





Major CAUSES of PAH

Idiopathic	Iatrogenic
C.Tissue D	Cirrhosis PortalH
COPD	CTEPH
Cong.Ht.D	Chronic Ht.F
Hemolytic A	HIV



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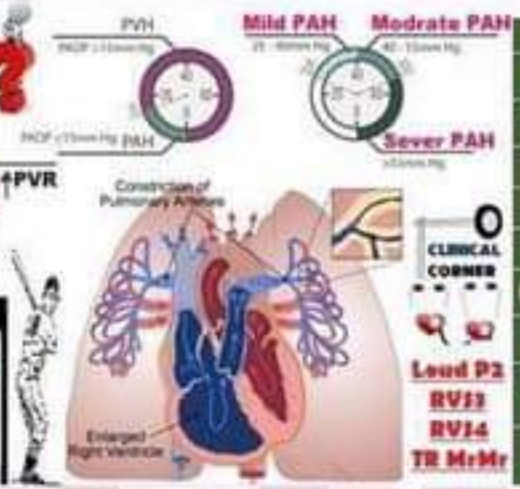

PROGNOSIS PH

Better prognosis	Worse prognosis
No RV Failure	+RV Failure
Slow Progression	Rapid Progression
No Syncope	+Syncope
WHO-FC I , II	WHO-FC IV
6MWT (>500 m)[a]	6MWT (<300 m)
Peak O2 >15	Peak O2 < 12
Normal BNP	Rising BNP
No Pericardial Effusion TAPSE[b] >2.0 cm	+ Pericardial Effusion TAPSE[b] <1.5 cm
RAP <8 mmHg and CI >2.5 L/min/m²	RAP >15 mmHg or CI ≤2.0 L/min/m²

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1. Introduction

Pulmonary arterial hypertension (PAH) is a serious disease of the arteries connecting the heart to the lungs (the pulmonary arteries). As PAH develops, blood flow through the pulmonary arteries is restricted and the right side of the heart is put under increasing strain to pump blood through to the lungs. This leads to the main symptoms of PAH – breathlessness, chest tightness limited exercise capacity and fatigue.

Untreated, PAH is a disease with a very poor prognosis.

The early symptoms of PAH (such as breathlessness, chest tightness and fatigue) can be mild and are common to many other conditions. Reaching the diagnosis can be delayed and as a consequence patients with PAH may first present when the disease has already progressed.

This brochure explains how PAH develops, describes the symptoms associated with this disease and outlines how it can be diagnosed and treated. Treatment is aimed at improving symptoms, exercise tolerance, long-term outcomes and quality of life. Until the mid-1980s there were limited treatment options for patients and PAH was associated with poor prognosis. Today, treatment options have improved the prognosis for patients with this condition.

2. What is PAH?

Pulmonary Arterial Hypertension (PAH) is a syndrome characterised by a progressive increase in pulmonary vascular resistance leading to right ventricular overload and eventually to right ventricular failure and premature death.[1]

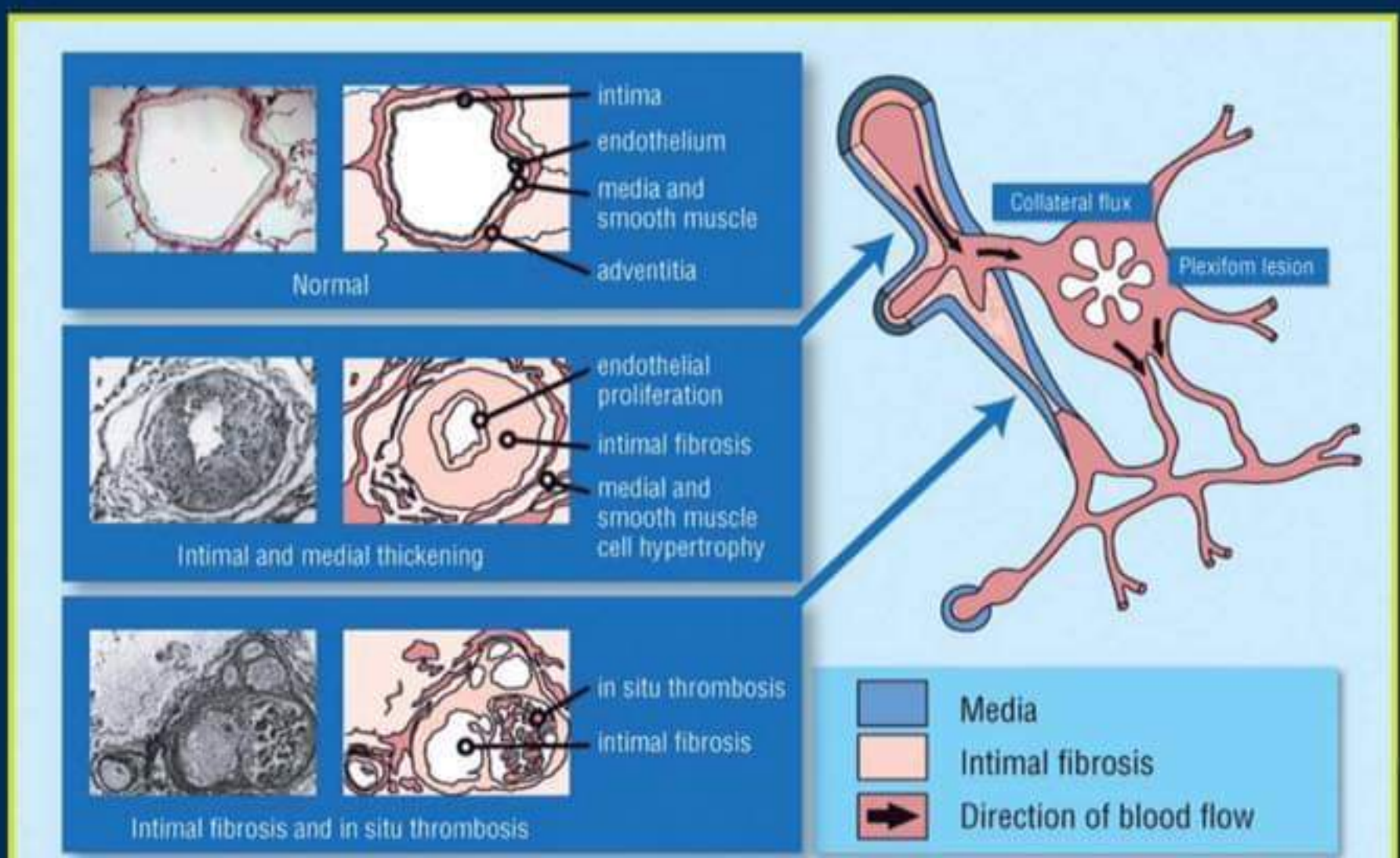
The increase in pulmonary vascular resistance is related to a number of progressive changes in the pulmonary arterioles, including:

- Vasoconstriction
- Obstructive remodelling of the pulmonary vessel wall through proliferation in the various layers of the blood vessel wall (smooth muscle cell and endothelial cell proliferation)
- Inflammation
- In-situ thrombosis

The main histological features include medial hypertrophy, intimal thickening, adventitial thickening, plexiform lesions and in-situ thrombosis (Figure 1). The plexifom lesion represents a focal proliferation of endothelial and smooth muscle cells and is pathognomonic of PAH.

PAH is defined as a sustained elevation of mean pulmonary arterial pressure to more than 25 mmHg at rest or to more than 30 mmHg while exercising, with a normal pulmonary wedge pressure (≤15 mmHg).[2] In most cases the earliest symptom is dyspnoea on physical exertion. Other symptoms include syncope or near syncope, fatigue and peripheral oedema.[3,4] Chest tightness and pain similar to angina may occur, particularly on physical exertion.

Figure 1.



3. Classification of PAH

Pulmonary Arterial Hypertension (PAH) represents Group 1 within the Pulmonary Hypertension WHO clinical classification system (Venice 2003 revision) and is one of five such groups. The groups are divided based on aetiology.[5]

Group I. Pulmonary arterial hypertension (PAH)
- Idiopathic (IPAH)
- Familial (FPAH)
- Associated with (APAH):
  - Connective tissue disease
  - Congenital systemic-to-pulmonary shunts
  - Portal hypertension
  - HIV infection
  - Drugs and toxins
  - Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary haemorragic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy)
- Associated with significant venous or capillary involvement
  - Pulmonary veno-occlusive disease (PVOD)
  - Pulmonary capillary haemangiomatosis (PCH)
- Persistent pulmonary hypertension of the newborn (PPHN)

Group II. Pulmonary hypertension associated with left heart diseases

Group III. Pulmonary hypertension associated with respiratory diseases and/or hypoxemia (including chronic obstructive pulmonary disease)

Group IV. Pulmonary hypertension due to chronic thrombotic and/or embolic disease

Group V. Miscellaneous group
- eg. sarcoidosis, histiocytosis X and lymphangiomatosis

Idiopathic PAH (IPAH), which by definition has no identifiable underlying cause, is one of the more common types of PAH. Familial PAH (FPAH) accounts for at least 6% of cases of IPAH and mutations in the bone morphogenetic protein receptor 2 (BMPR2) have been identified in the majority of cases of FPAH.[6,7]

PAH can also be associated with a number of conditions (Associated Pulmonary Arterial Hypertension – APAH), which together account for most other cases of PAH. These conditions include:

1. Connective Tissue Diseases
   - including systemic sclerosis (scleroderma) and systemic lupus erythematosus (SLE)
2. Congenital Heart Disease
   - including Eisenmenger's syndrome
3. Human immunodeficiency virus (HIV) infection
4. Sickle Cell Disease

1. PAH associated with connective tissue disease

PAH is a well-recognised complication of connective tissue diseases such as systemic sclerosis and SLE and in affected patients may also occur in association with interstitial lung disease. The prevalence of PAH in patients with systemic sclerosis has been reported to be up to 16%[8] and in systemic sclerosis patients, pulmonary complications, such as interstitial lung disease and PAH, are now the leading causes of death. Patients with PAH associated with systemic sclerosis have a particularly poor prognosis compared to those with systemic sclerosis without PAH.[9]

2. PAH associated with congenital heart disease

Congenital heart disease is relatively common, affecting around 1% of the population. Within this population 15% will go on to develop PAH.[10] As determined by the level of pulmonary vascular resistance, the most severe form of PAH is Eisenmenger's syndrome, which is associated with the reversal of an initial left to right shunt causing cyanosis and limited exercise capacity.[11]

3. PAH associated with HIV infection

PAH is a rare (estimated prevalence in patients with HIV: 0.5%)[12] but relatively well-documented complication of HIV infection. With the advent of highly active anti-retroviral therapy (HAART) and markedly improved survival, PAH and other non-infectious manifestations of HIV infection are increasingly responsible for HIV-associated morbidity and poor prognosis. In patients with HIV, the HIV-1 envelope glycoprotein GP120 may stimulate the production of endothelin by macrophages.[13] HIV-associated PAH shows a similar clinical picture to IPAH and seems to be independent of the degree of immunosuppression.

4. PAH associated sickle cell disease

Sickle cell disease (SCD) is a genetic disorder of the haemoglobin which results in a chronic haemolytic anaemia. Over time and due to the chronic haemolysis the vasculature becomes damaged and pulmonary hypertension can develop. The prevalence of PAH in sickle cell patients is 20–40%.[14] The two year mortality rate of pulmonary hypertension related to SCD is reported up to 50% and is one of the leading causes of death in SCD.[15]

6. Why does PAH develop?

The exact cause behind the development of PAH remains unknown. However, research has led to a better understanding of the underlying mechanisms.

PAH is recognised as a complex, multi-factorial condition involving numerous biochemical pathways and different cell types. Endothelial dysfunction is believed to occur early on in disease pathogenesis, leading to endothelial and smooth muscle cell proliferation and structural changes or 'remodelling' of the pulmonary vascular bed resulting in an increase in pulmonary vascular resistance.

Vascular remodeling itself involves all layers of the vessel wall and is characterised by proliferative and obstructive changes involving many cell types, including endothelial, smooth muscle and fibroblasts. Inflammatory cells and platelets may also play a significant role in PAH.

Endothelial cell dysfunction results in reduced production of vasodilators,such as **nitric oxide (NO)** and **prostacyclin**, and over production of vasoconstrictors, such as **thromboxane A2** and **endothelin-1 (ET-1)**.

ET-1, NO and prostacyclin have been the principal focus of research into new treatment options for patients with PAH.

Endothelin

Endothelin is produced by the endothelial cells and is essential for maintenance of normal vascular tone and function. However, high levels of endothelin are seen in patients with PAH due to various aetiologies[18-20] and correlate with disease severity,[21] resulting in a number of detrimental effects, primarily in the vasculature:[3]

- **Fibrosis**
- **Hypertrophy** and **proliferation** of cells, which can lead to thickening, narrowing and occlusion of blood vessels
- **Inflammation**
- **Vasoconstriction**

Endothelin binds to 2 receptors, ET_A and ET_B. Both receptors are implicated in PAH and mediate the deleterious effects of endothelin.[22] 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.

Prostacyclin

Prostacyclin is a potent vasodilator as well as an inhibitor of platelet activation.

It is believed that patients with PAH have low levels of prostacyclin, which could result in vasoconstriction in the pulmonary vasculature and a tendency for smooth muscle cell proliferation and platelet activation, encouraging the formation of thrombi in both the micro-circulation and the pulmonary arteries.[23-25] Therapy with synthetic forms of prostacyclin can help to correct this deficiency, although administering this form of treatment is complex.[26-28]

9. How is PAH diagnosed?

The non-specific nature of symptoms associated with PAH means that the diagnosis cannot be made on symptoms alone. A series of investigations is required to make an initial diagnosis, to refine that diagnosis in terms of clinical class of pulmonary hypertension and to evaluate the degree of functional and haemodynamic impairment (Figure 2). Consequently, it can be useful to adopt a four stage approach:

1. Clinical suspicion of pulmonary hypertension

- Breathlessness (dyspnoea) without overt signs of specific heart or lung disease
- Screening of patients with associated conditions (Connective Tissue Disease, Congenital Heart Disease, HIV, Sickle Cell Disease)
- Incidental findings on examination for other clinical reasons

2. Detection of pulmonary hypertension

- ECG (echocardiogram)
- Doppler echocardiogram (Figure 2)
- Chest radiograph, may show evidence of cardiomegaly and enlarged pulmonary arteries (Figure 3)

3. Identify other causes of pulmonary hypertension

- Pulmonary function tests (PFTs) and arterial blood gas samples
- Ventilation and perfusion lung scan
- High resolution computed tomography (HRCT)
- Pulmonary angiography

4. PAH evaluation and classification (type, functional capacity, haemodynamics)

- Blood tests and immunology, HIV test, abdominal ultrasound scan
- 6 minute walk test (6-MWT) and peak VO2
- Right heart catheterisation and vasoreactivity testing

Figure 2.

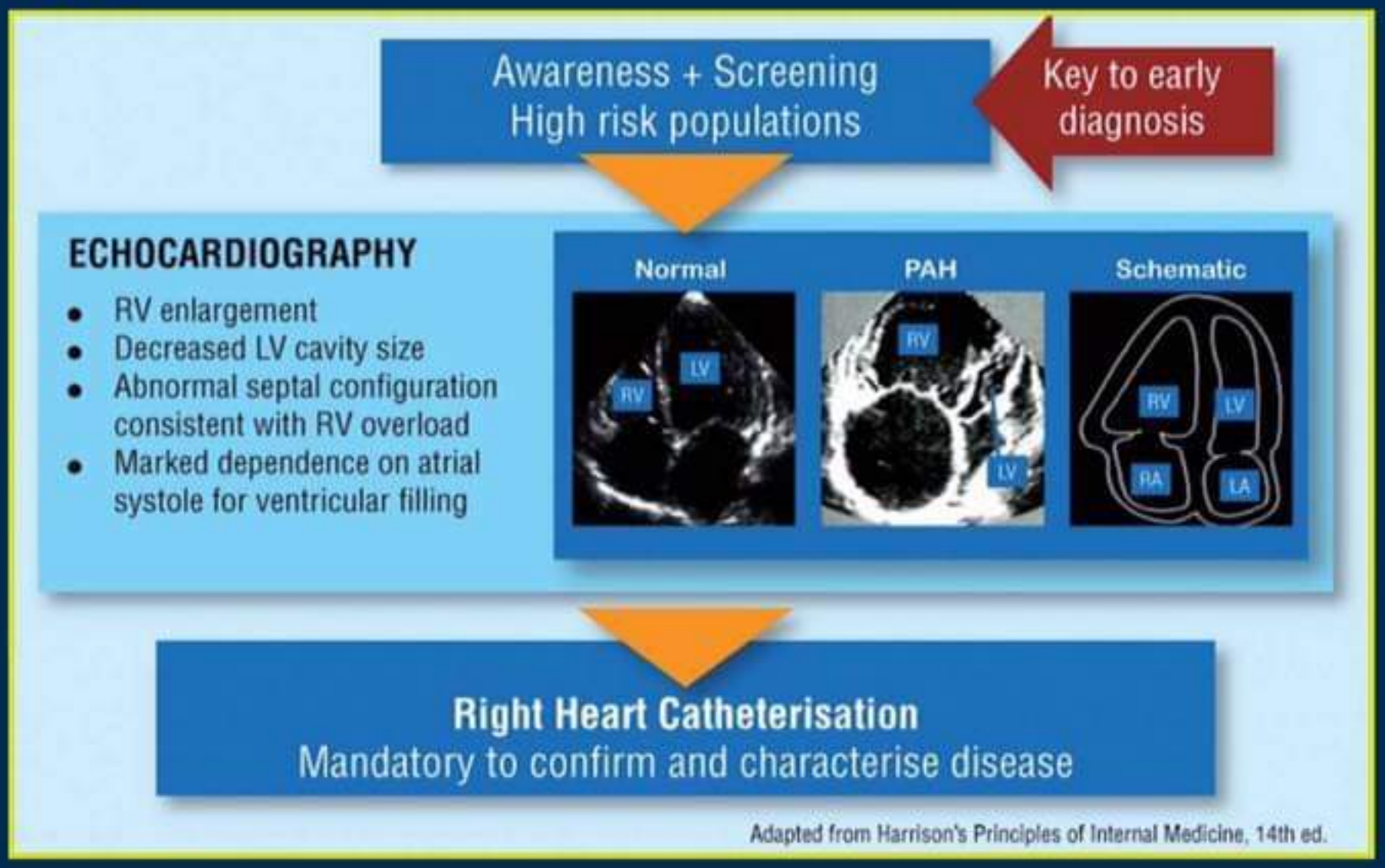
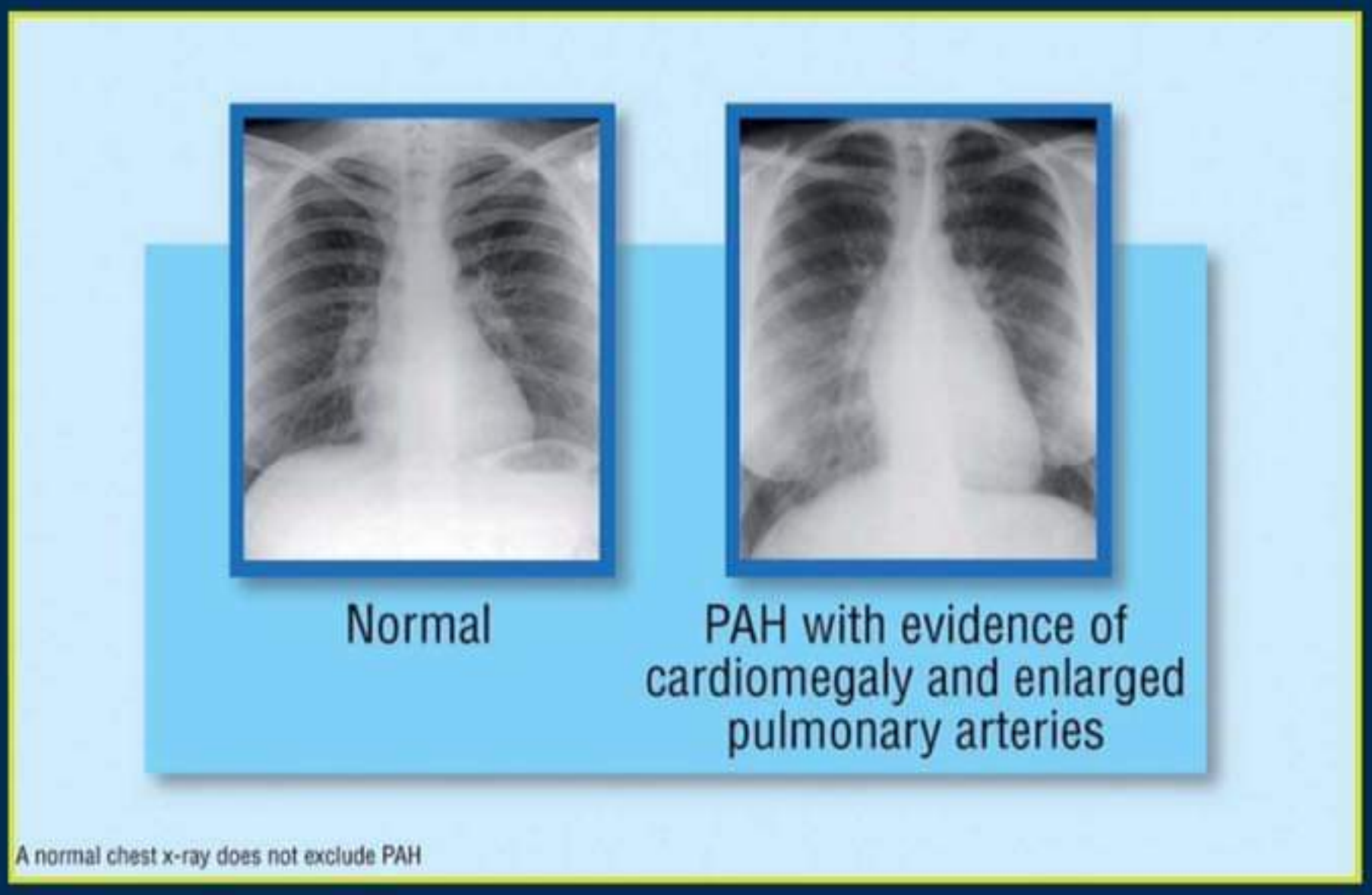


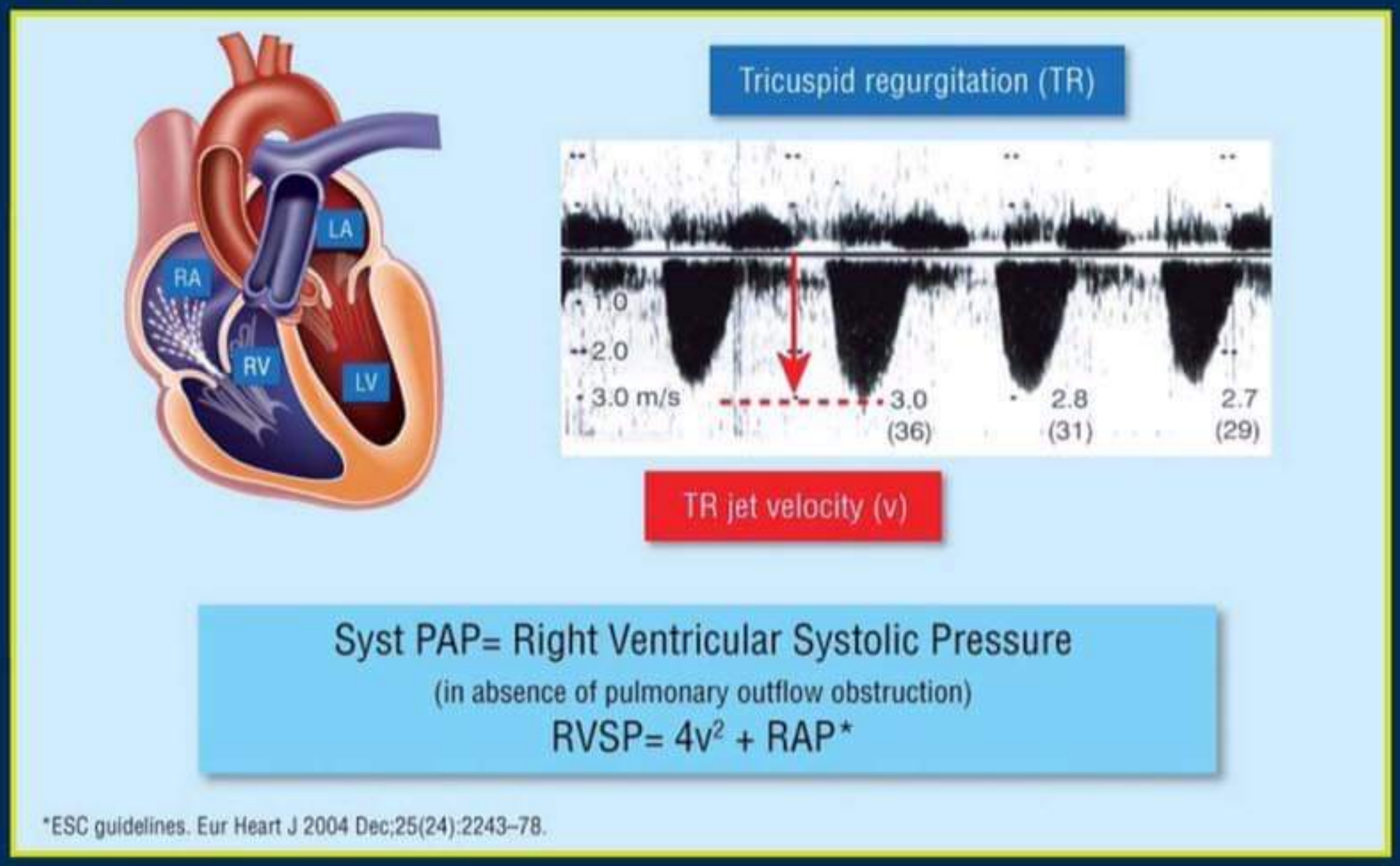
Figure 3.



11. Echocardiography – value as a screening tool

Transthoracic Doppler-echocardiography (TTE) is a non-invasive screening test for pulmonary arterial hypertension. TTE is able to estimate pulmonary arterial systolic pressure, which is equivalent to right ventricular systolic pressure in the absence of pulmonary outflow obstruction. It can provide additional information about the cause and consequences of PH, including right and left ventricular dimensions and function, heart valve abnormalities, right ventricular ejection and left ventricular filling characteristics and presence of a pericardial effusion. **In the initial investigation of patients with PAH it is important to obtain adequate images of the right heart**. Pulmonary arterial pressure can be estimated from the tricuspid regurgitant (TR) jet (Figure 5).

Figure 5.



*ESC guidelines. Eur Heart J 2004 Dec;25(24):2243–78.

10. Screening in PAH: key to early diagnosis

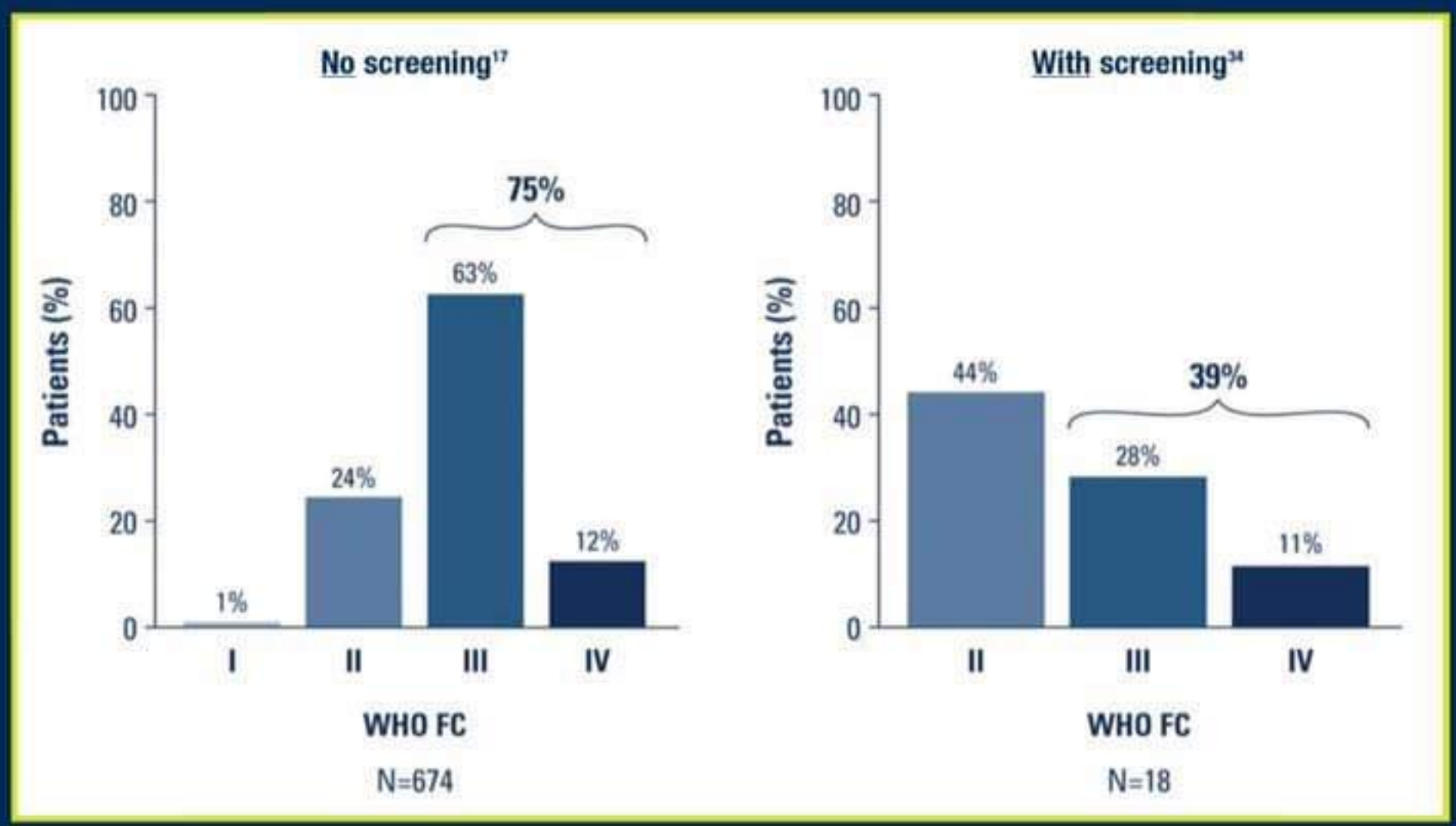
The key to early diagnosis is introducing screening for high risk patient populations if they are asymptomatic. High risk patient populations include:

- Family members of a patient with familial Pulmonary Arterial Hypertension (FPAH)
- Patients with systemic sclerosis (SSc)
- Patients with HIV
- Patients with portopulmonary hypertension (PoPH)

The results of a disease registry in France indicated that without screening, the majority of patients were diagnosed in a more severe stage of PAH (WHO FC III/IV), and only 25% of patients were in early stage PAH (WHO FC I/II).[17] Furthermore, the results of a French national screening program in a high-risk population indicated that it is possible to detect Pulmonary Arterial Hypertension (PAH) in an earlier stage in a high-risk population[34] (Figure 4).

International guidelines now recommend annual screening high-risk groups with Doppler echocardiography.[2,8,35] Doppler echocardiography is currently the most effective method for screening, however, for a definitive diagnosis right heart catheterisation has to be performed.

Figure 4.



12. Right heart catheterisation – the diagnostic gold standard

Right heart catheterisation is required for a definitive diagnosis of PAH (Figure 6 and 7)[3,4] to assess the severity of haemodynamic impairment and to test the vasoreactivity of the pulmonary circulation. The following parameters should always be assessed: right atrial pressure (RAP), pulmonary arterial pressure (PAP [systolic, diastolic and mean]), pulmonary capillary wedge pressure (PCWP), cardiac output/index, pulmonary (PVR) and systemic vascular resistance, blood pressure and arterial and mixed venous oxygen saturation.

PAH is defined as a sustained elevation of mean pulmonary arterial pressure to >25 mmHg at rest or to >30 mmHg while exercising, with a mean pulmonary wedge pressure or left ventricular end-diastolic pressure of ≤15 mmHg and pulmonary vascular resistance of ≥3 woods units.[2] A positive vasoreactive response is defined as a reduction in mean pulmonary artery pressure (mPAP) ≥10 mmHg to reach an absolute value of mPAP ≤40 mmHg with an increase or unchanged cardiac output. A positive response is shown in only 10–15% of patients, and sustained response is shown in even fewer (less than 7%).[1]

Figure 6.

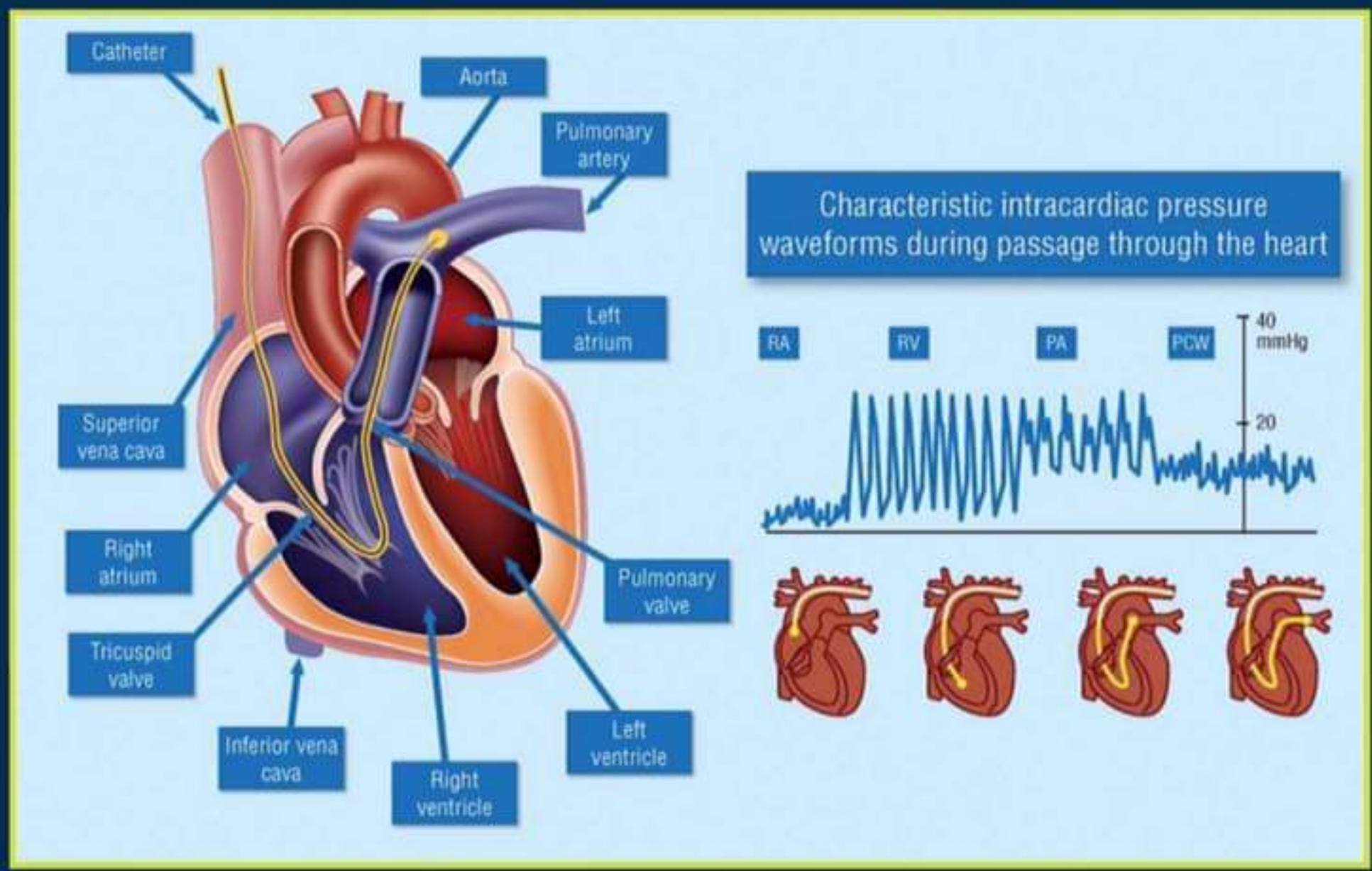


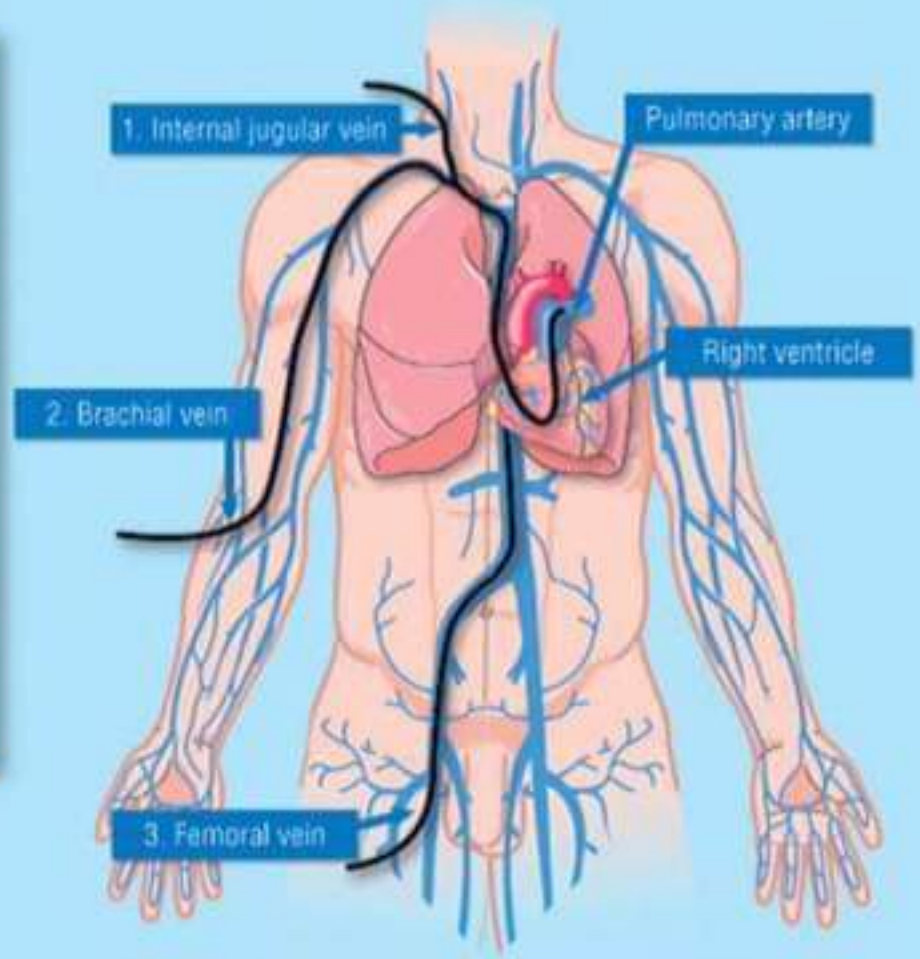
Figure 7.

Right heart catheterisation is required to confirm the diagnosis of PAH.

PAH is defined by

- mPAP > 25 mmHg at rest
- mPAP > 30 mmHg with exercise
- PCWP ≤ 15 mmHg
- PVR > 3 units

Cardiac output is also required to calculate PVR.



Standard approaches for catheter access

Barst, JACC 2004 vol.43 N. 12

13. Assessing PAH: 6-minute walk test – an evaluation of exercise capacity

In patients with PAH, the 6-MWT to evaluate exercise capacity is reflective of activities of daily living;[36] the distance a PAH patient can walk in 6 minutes is a critical endpoint in studies evaluating the benefit of different therapeutic options.

To allow meaningful comparisons, it is important that the 6-MWT be performed under supervision according to a standardised protocol.[37]

- A 30 m corridor should be available, marked at 3 m intervals
- The patient should rest for at least 10 minutes prior to the test and should not have performed any rigorous exercise within the previous 2 hours
- The patient should be asked to rate their baseline dyspnoea
- The patient should be instructed to walk to their maximum capacity but not to run or jog; they should be permitted to rest as necessary
- The supervisor should count each lap as the patient finishes it
- The patient should be asked to rate their dyspnoea at the end of the test
- The test should be repeated at approximately the same time of day on each occasion

14. How is PAH treated?

There is currently no cure for PAH but advances in understanding how the disease develops (see section: Why does PAH develop?) means that there are now treatments available which have helped to improve prognosis for patients with this disease.

Prognosis is influenced by the status of WHO FC when treatment is started – patients who start therapy in functional class I or II demonstrate a better prognosis than those whose therapy is started in more severe stages (WHO FC III or IV).[33]

Early treatment may delay disease progression

By recognising and treating patients as early as possible, disease progression may be delayed. Without treatment, patients in WHO FC II can rapidly deteriorate within 6 months to more advanced Pulmonary Arterial Hypertension (PAH) as evidenced by progression of symptoms.[38]

Treatment options have progressed considerably in the last decade, especially those which target the underlying mechanisms of the disease. The main medical treatment options for patients with PAH are:[39]

Treatments that are routinely used but with little evidence of a positive impact on the disease progression

- Anticoagulants, such as warfarin, to address the observed thrombotic changes and potential predisposition in the pulmonary microcirculation for in-situ thrombosis
- Calcium-channel blockers (CCBs). Less than 10% of IPAH patients benefit from CCB therapy. This figure is even lower in other forms of PAH. If not used in appropriate candidates (patients with demonstrated vasoreactivity during right heart catheterisation), CCBs can decrease cardiac output and systemic vascular resistance without any improvement in PAP and PVR and therefore may be deleterious[1]
- Diuretics, for treatment of right heart failure
- Oxygen therapy, to maintain oxygen saturation at >90% at all times

Treatments that have been specifically studied in PAH

- **Endothelin receptor antagonists** – endothelin is implicated in the pathogenesis of PAH through actions on the pulmonary vasculature. Endothelin is found to be elevated in patients with PAH and levels of endothelin are directly related to disease severity and prognosis. Endothelin receptor antagonists (ERAs) are oral treatments that either block the ET_A receptor alone or both the ET_A and ET_B receptors[22]
- **Phosphodiesterase 5 inhibitors** – oral agents which induce relaxation and antiproliferative effects on vascular smooth muscle cells by preventing the reduction in levels of cGMP[29]
- **Prostacyclin analogues** – may be delivered by continuous intravenous or subcutaneous infusion or via an intermittent nebuliser[39]

In very severe cases surgical options may be considered:

- Balloon atrial septostomy
- Heart and lung transplantation

However, the use of transplantation is constrained by the limited number of donor organs.