THE NORTHERN HOSPITAL

PULMONARY HYPERTENSION

"Her Cross", oil on canvas, 1915, Lawson Wood

"...And though you died back in 1916, To that loyal heart you're forever nineteen...."

"The lamps are going out all over Europe, I fear we shall not see them lit again in our life-time"

British Foreign Secretary Sir Edward Grey, 3rd August 1914

They were summoned from the hillside,
They were called in from the glen,
And the country found them ready
At the rallying call for men

Let no tears add to their hardships
As the soldiers pass along,
And although your heart is breaking,
Make it sing this cheery song:

Keep the Home Fires Burning,
While your hearts are yearning.
Though your lads are far away
They dream of home.
There's a silver lining

Through the dark clouds shining,
Turn the dark cloud inside out
Till the boys come home.
Overseas there came a pleading,
"Help a nation in distress".

And we gave our glorious laddies -
Honour bade us do no less,
For no gallant son of Freedom
To a tyrant's yoke should bend,

And a noble heart must answer
To the sacred call of "Friend".

Keep the Home Fires Burning,
While your hearts are yearning.
Though your lads are far away

They dream of home.
There's a silver lining

Through the dark clouds shining,
Turn the dark cloud inside out
'Til the boys come home

"Keep the Home Fires Burning,
Till the Boys Come Home", 1914,
Lena Guilbert Ford

Oh how do you do, young Willy McBride Do you mind if I sit here down by your graveside, And rest for a while in the warm summer sun. I've been walking all day, and I'm nearly done

And I see by your gravestone you were only nineteen, When you joined the great fallen in 1916. Well I hope you died quick And I hope you died clean Or Willy McBride, was is it slow and obscene.

Did they beat the drums slowly
Did they play the fife lowly. Did they sound the death march as they lowered you down, Did the band play the last post and chorus, Did the pipes play the flowers of the forest

And did you leave a wife or a sweetheart behind In some loyal heart is your memory enshrined And though you died back in 1916 To that loyal heart you're forever nineteen Or are you a stranger without even a name Forever enshrined behind some old glass pane, In an old photograph torn, tattered, and stained And faded to yellow in a brown leather frame

Did they beat the drums slowly, Did they play the fife lowly, Did they sound the death march as they lowered you down Did the band play the last post and chorus, Did the pipes play the flowers of the forest. The sun shining down on these green fields of France. The warm wind blows gently and the red poppies dance. The trenches have vanished long under the plow. No gas, no barbed wire, no guns firing now

But here in this graveyard that's still no man's land. The countless white crosses in mute witness stand, To man's blind indifference to his fellow man, And a whole generation were butchered and damned

Did they beat the drums slowly, Did they play the fife lowly, Did they sound the death march as they lowered you down, Did the band play the last post and chorus, Did the pipes play the flowers of the forest

And I can't help but wonder oh Willy McBride, Do all those who lie here know why they died. Did you really believe them when they told you the cause
Did you really believe that this war would end wars Well the suffering, the sorrow, the glory, the shame The killing and dying it was all done in vain Oh Willy McBride it all happened again
And again, and again, and again, and again

Did they beat the drums slowly, Did they play the fife lowly, Did they sound the death march as they lowered you down, Did the band play the last post and chorus, Did the pipes play the flowers of the forest...

Eric Bogle, "The Green Fields Of France", 1976

Perhaps two songs separated by a gulf of nearly three quarters of a century best sum up the tragedy of the Great War - Lena Guilbert Ford, summed up the sentiment at the outbreak of the conflict.....but no one could adequately sum it up at the end....there was simply a great silence. It would only be in far distant retrospect that the full scale of the catastrophe could be more fully appreciated.

At its outbreak in 1914 there was unbounded enthusiasm - all sides confident of quick and assured victory, although the British Foreign Secretary Sir Edward Grey wasn't so

sure that the coming conflict would be so quick and so clean. It would be the first war fought between superpowers in the modern age, and it would be fought with modern weapons on an unprecedented industrial scale. Stirring patriotic songs, encouraged young men to enlist. Lena Guilbert Ford, most famously encouraged their mothers! Four years of shocking bloodletting followed that saw a whole generation of young men on both sides butchered and damned. There was no "victory" by anyone - in the words of Juliet Nicolson the Great War was followed not by celebration or even relief, but in truth by a "Great Silence". The true cost could barely be comprehended let alone contemplated, it was simply too painful. In 1976 the Scotts-Australian Eric Bogle sat down beside the grave of an unknown 19 year old soldier of the War, in deep reflection. He later produced one of the great Celtic Ballads - "The Green Fields Of France", by which he finally gave answer to Lena Guilbert Ford – the home fires were kept burning, but for millions the boys never came home, and there was no silver lining even for those who did come home, only the silent tears.

For patients who develop pulmonary hypertension the situation is foreboding. There may be some "small silver lining" - it all depends on the exact aetiology. But for those who develop right heart failure or Eisenmenger's syndrome; the lights are surely going out.

PULMONARY HYPERTENSION

Introduction

Pulmonary arterial hypertension is technically defined as a *mean* pulmonary artery pressure of **greater** than: [4]

- **25 mm Hg** at rest

Or

- **30 mm Hg** with exercise

as recorded during right heart catheterization.

Although pulmonary hypertension can be measured on echocardiography, the gold standard for diagnosis is right heart catheterization.

It can be primary or it can be due to secondary causes.

Its presence usually portends a poor prognosis.

Pathology

The causes of pulmonary arterial hypertension have traditionally been described as:

1. Primary (or Idiopathic)

Essentially this means pulmonary hypertension of unknown cause.

There is a primary elevation of pressure in the pulmonary arterial system alone (i.e. a **pulmonary arterial hypertension**).

It may be an inherited condition or an acquired condition.

2. Secondary causes:

This is pulmonary hypertension due to a known pathology. It is secondary to elevations of pressure in the pulmonary **venous** and pulmonary **capillary** systems (**pulmonary venous hypertension**).

Causes include:

- Recurrent pulmonary emboli
- Chronic lung disease:
  - ♥ Asthma
  - ♥ COPD
  - ♥ Pulmonary fibrosis (**of any cause**)
  - ♥ Obstructive sleep apnoea:
    - ♥♥ Untreated OSA alone is associated with only mild PH. However, it may be associated with significant PH when combined with obesity hypoventilation syndrome or another cause of hypoxaemia.

      These patients have a significant risk of mortality due to progressive pulmonary hypertension, cor pulmonale, or arrhythmias, although the exact magnitude of the risk is uncertain
  - ♥ Chronic exposure to high altitude.
- Chronic heart disease:
  - ♥ Left sided heart disease, in particular, left valvular (i.e. mitral and aortic) disease.

    There is elevated left atrial (e.g. mean pressure >14 mmHg) with secondary elevations in the pulmonary venous pressure (pulmonary venous hypertension).

- ♥ Uncorrected congenital heart disease with left to right shunting, **(Eisenmenger's Syndrome**):
  - ♥♥ ASDs
  - ♥♥ VSDs
  - ♥♥ Patent Ductus Arteriosus
- Severe kyphoscoliosis.

Complications

1. Right heart failure with consequent chronic hypoxia.
2. Arrhythmias
3. Polycythaemia (haemoglobin level > 170 g/L)

Prognosis is varies according to the nature and extent of the underlying disease.
Patients with **severe pulmonary artery hypertension** or **right heart failure (i.e., cor pulmonale)** have a very poor prognosis and without treatment usually die within one year.

The WHO Classification of Pulmonary Hypertension [5]

More recently it has been recognized that some types of "secondary" pulmonary hypertension more closely resemble idiopathic pulmonary hypertension.

As such the World Health Organization (WHO) has re-classified pulmonary hypertension based upon **etiology** and **mechanism** into **five principal groups** listed below.

Pulmonary arterial hypertension (PAH) refers to group 1 PAH.

Pulmonary hypertension (PH) refers to any of group 2 through group 5 PH, (and is also used generically when referring to all five groups collectively).

Group 1: Pulmonary arterial hypertension (PAH):

- Pulmonary arterial hypertension (PAH) consists of sporadic idiopathic PAH (IPAH), heritable PAH (also known as familial PAH), and PAH due to diseases that **localize** to the **small pulmonary muscular arterioles.**

  These include PAH due to drugs and toxins, connective tissue diseases, HIV infection, portal hypertension, congenital heart disease, and schistosomiasis.

Group 2: PH due to left heart disease:

- PAH can develop in patients with left to right intracardiac shunts (atrial, ventricular, and great artery defects), especially when they are large and nonrestrictive, due to increased pulmonary blood volume or pressure overload.

  Eisenmenger syndrome is the most severe and end-stage form of shunt-related PAH.

Group 3: PH due to chronic lung disease and/or hypoxemia

- PH is a common complication of COPD.

Group 4: Chronic thromboembolic pulmonary hypertension:

- Chronic thromboembolic pulmonary hypertension (CTEPH) is due to chronic thromboembolic occlusion of the proximal or distal pulmonary vasculature. PAH in this group has the potential for improvement or cure with pulmonary thromboendarterectomy.

  All patients with PH, including this group, are at risk of pulmonary embolus.

Group 5: PH due to unclear multifactorial mechanisms

Clinical Features

Important points of History:

The presenting symptoms of pulmonary hypertension are nonspecific and so frequently result in a delay in diagnosis.

Essentially symptoms relate to hypoxia and right heart failure, and so in general terms may include:

1. Exertional dyspnoea

2. Increasing lethargy / malaise

3. Chest pain:

   - Exertional chest pain (i.e., angina) is usually due to subendocardial hypoperfusion caused by increased right ventricular wall stress and myocardial oxygen demand.

4. Syncope:

- In particular exertional syncope which is due to the inability to increase cardiac output during activity or reflex bradycardia that is secondary to mechanoreceptor activation in the right ventricle.

Important points of Examination:

The classically described signs of pulmonary hypertension include: [4]

1. General inspection:

   In severe disease there may be obvious:

   - Tachypnoea
   - Cyanosis (peripheral and/ or central)

2. Pulse:

   - In severe disease the pulse will be of low volume.

3. JVP:

   - A prominent "a" wave may be seen, due to forceful atrial contraction.

4. Cardiac auscultation:

   Heart sounds:

   - There may be a loud S2, (this is due to a loud pulmonary component of the second heart sound
   - There may be an S4

   Murmurs:

   - There may be a pulmonary ejection systolic flow murmur.
   - There may be a diastolic pulmonary regurgitation murmur, if there is significant dilation of the pulmonary artery.

5. Apex beat:

   - There may be a palpable right ventricular heave
   - There may be a palpable second heart sound

6. **Cor pulmonale:**

- In late cases of severe disease there may be signs of **right heart failure.**

Functional assessment of the patient with Pulmonary Hypertension:

Functional assessment is required to provide prognostic information and also to assess suitability for specific pulmonary hypertension therapies.

The World Health Organization (WHO) functional classification may be used and is shown in the table below:

WHO functional class	Symptoms
Class I	Minimal symptoms (dyspnoea, chest pain, fatigue, presyncope) that do not limit physical activity
Class II	Symptoms resulting in a slight limitation of physical activity
Class III	Symptoms resulting in marked limitation of physical activity
Class IV	Symptoms resulting in the inability to carry out physical activity

Investigations

Blood tests

Depending on the nature of the presentation, the following may be considered:

1. FBE
2. CRP
3. U&Es/ glucose
4. ABGs/ VBGs

Others according to the suspicion for any given underlyinhg pathology.

ECG

Electrocardiographic features seen in pulmonary hypertension include:

1. Sinus tachycardia

2. Non-specific signs of right heart strain/ hypertrophy:

    - P pulmonale
    - RBBB pattern
    - Dominant R waves in early chest leads
    - Right axis deviation.

3. Arrhythmias:

    The following are common: [4]

    - Atrial Fibrillation
    - Multifocal atrial tachycardia

CXR

This is useful as an initial screen for lung disease, in particular interstitial lung disease (pulmonary fibrosis) or COPD

It is also useful for assessment of the cardiac silhouette, as a possible indicator of cardiac disease:

Indirect indicators of right ventricular disease include:

- Right ventricular dilation, (on A-P or lateral views)
    - ♥ Right ventricular enlargement however may be difficult to detect because of lung hyperinflation.
- Enlarged proximal pulmonary arteries with peripheral "pruning".

CT Scan

High resolution CT scan is required to assist in diagnosing the nature and extent of causative lung pathology.

Echocardiography

Although pulmonary hypertension can be measured on echocardiography, the gold standard for diagnosis is still considered to be measurement via right heart catheterization.

Transthoracic echocardiography is the best initial non-invasive method of assessing pulmonary hypertension but image quality may be reduced by lung hyperinflation. Trans-oesophageal echocardiography may be required.

It measures the **peak pulmonary artery pressure** rather than the mean pressure.

An elevation of *peak* pulmonary artery pressure of greater than **40 mm Hg** indicates pulmonary hypertension.

Right ventricular dilation and abnormal septal motion are also indicators of pulmonary hypertension.

The severity of pulmonary hypertension may however be overestimated by echocardiography, especially in high cardiac output states, and cardiac catheterisation is required to confirm the diagnosis before prescribing specific therapies for pulmonary hypertension.

Cardiac catheterisation:

Pulmonary hypertension is technically defined as a *mean* pulmonary artery pressure of greater than **25 mm Hg at rest or 30 mm Hg with exercise**, recorded during right heart catheterisation.

Cardiac catheterisation is therefore considered to be the "gold standard" investigation required to make a definitive diagnosis.

It is also useful for ruling out co-existent coronary artery disease.

Lung Function Tests

These may used to confirm the nature and extent of lung disease

PH should not be attributed to lung disease if the pulmonary function tests, including diffusion abnormalities, are only mildly abnormal.

Management

With respect to ED presentations of patients with pulmonary hypertension, issues will include:

1. Immediate resuscitation; guided often by prior "Limitation of Medical Therapy Directives"

2. Investigation and management of any underlying precipitating factors

3. Review of medications directed toward the precipitating factor as well as any agents directed against the pulmonary hypertension itself.

4. Assessment of the patient's functional status and ability to cope at home, and hence the need for admission to hospital.

Immediate resuscitation

Oxygen therapy should be administered if it provides symptomatic relief.

Hypoxaemia can worsen pulmonary arterial hypertension, and oxygen should be used if the patient has hypoxaemia.

Long term, continuous (>15 hour /day) oxygen therapy to treat chronic hypoxaemia prolongs survival of patients with COPD, presumably by reducing pulmonary hypertension. [4]

Investigation and management of any underlying precipitating factors

Precipitating factors should be sought and treated as indicated, in particular consider the possibilities of:

- Sepsis
- Acute coronary syndrome
- Pulmonary embolism
- Bacterial endocarditis, especially in cases of known valvular heart disease.

Review of medications directed toward the pulmonary hypertension itself.

Medications used in the treatment of patients with pulmonary hypertension will depend on the underlying pathology and the severity of the disease as well as any specific contra-indications a patient may have.

In *general terms* the following medications are used: [1, 4]

1. Diuretics:
    - Should be used if there is right heart failure, particularly if oedema is present.
    - Diuretics may reduce right ventricular filling pressure and oedema, but excessive volume depletion must be avoided. Volume status can be monitored by measuring serum creatinine and urea levels.
    - Diuretics may cause metabolic alkalosis resulting in suppression of ventilatory drive.

2. Digoxin:

- This is often prescribed in the presence of right heart failure or a low cardiac output, (although data concerning its efficacy in this setting are lacking).

- In general digoxin is **not specifically** indicated in the treatment of cor pulmonale and may increase the risk of arrhythmia when hypoxaemia is present.[4]

- It **may** be used to control the **rate** of chronic atrial fibrillation.[4]

3. Calcium channel blockers:

In general vasodilators (hydralazine, nitrates, nifedipine, verapamil, diltiazem, angiotensin-converting enzyme inhibitors) do **not** produce **sustained** relief of pulmonary hypertension in patients with COPD. [4]

In fact they can worsen oxygenation (by increasing blood flow through poorly ventilated lung) and result in systemic hypotension. [4]

A **small proportion** of patients with pulmonary arterial hypertension may benefit from calcium channel blockers.

A cautious trial under specialist supervision may be used in patients with severe or persistent pulmonary hypertension not responsive to home oxygen therapy. [4]

A trial of calcium channel blockade is worthwhile in these patients, but should be **discontinued** if there is no clinical improvement. [1]

Verapamil should **not** be used because of its significant negative inotropic effects.

The following agents have been used:

- Amlodipine

- Diltiazem

- Felodipine

- Lercanidipine

- Nifedipine

See latest Cardiovascular Therapeutic Guidelines for full prescribing details.

4. Anticoagulation:

Pulmonary arterial and arteriolar thrombosis can complicate pulmonary hypertension and worsen its severity.

There is evidence that anticoagulant therapy improves outcome, particularly in idiopathic pulmonary arterial hypertension, but overall this evidence is not strong.

Nonetheless, anticoagulation with warfarin is usually recommended if the risk of bleeding is low.

Use warfarin, with a target INR of 2 to 3.

5. Specific pulmonary arterial hypertension therapies:

There are three classes of drugs with some evidence of efficacy in pulmonary arterial hypertension from randomized controlled trials. These are: [1]

- Endothelin receptor antagonists
- Prostanoid analogues
- Phosphodiesterase type 5 (PDE5) inhibitors.

These drugs may only be prescribed through Section 100 of the Pharmaceutical Benefits Scheme (PBS) if specific criteria are met, and only through designated prescribing centres. These agents are prescribed by specialist cardiologists or respiratory physicians.

Extensive clinical and laboratory testing, including right heart catheterization, is required, as is referral to a pulmonary hypertension unit at a designated prescribing centre.

The combination of these specific therapies may confer additional benefit.

6. Surgery:

- Occasionally, some patients with severe disease unresponsive to therapy may be suitable for consideration of lung or heart-lung transplantation or right to left shunts.

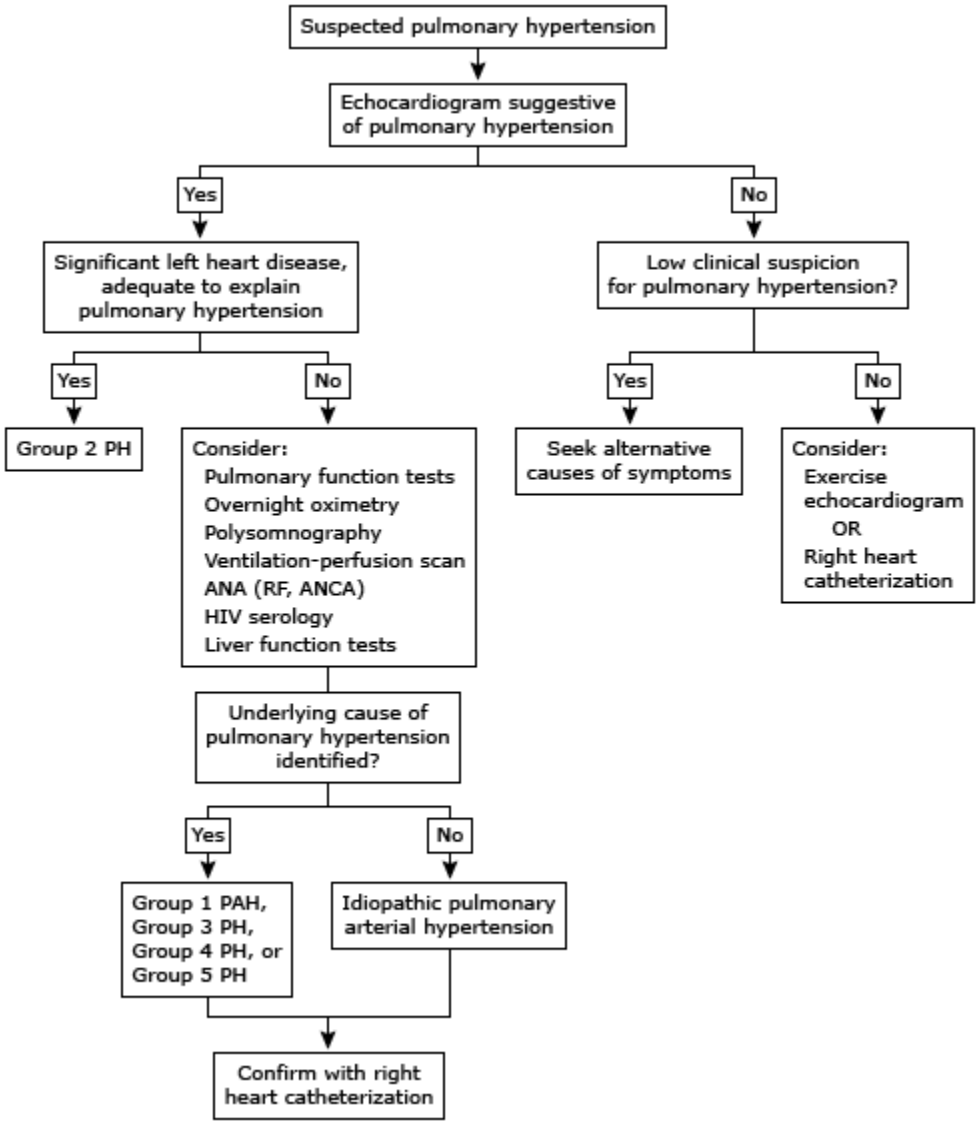
Disposition:

There should always be an assessment of the patient's **current functional status** and ability to cope at home. This is an important consideration in any patient with pulmonary hypertension who presents to the ED.

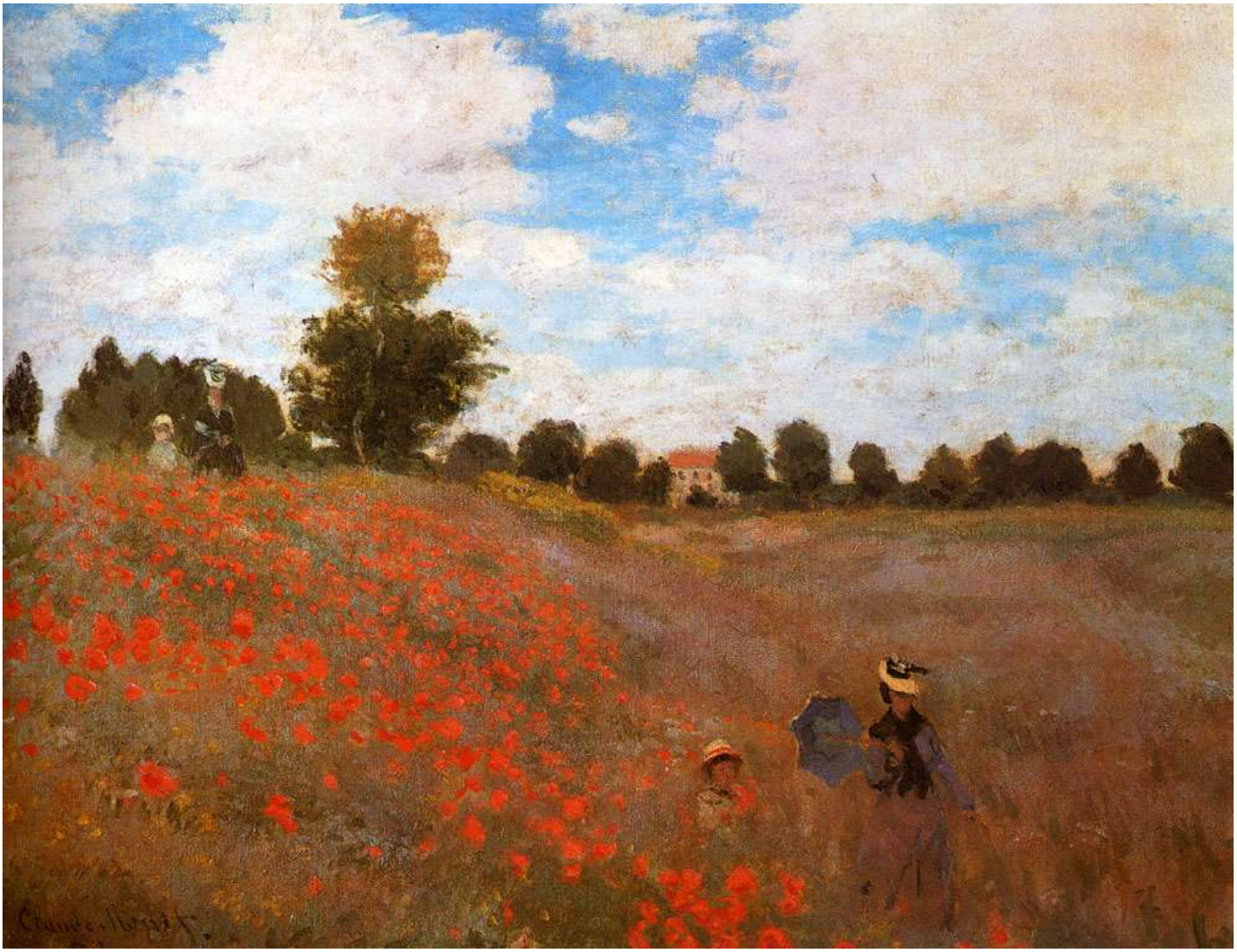
Hospital admission will often be required on this basis alone, even if an obvious precipitating event cannot be found.

Appendix 1

Investigation of Suspected Pulmonary Hypertension:



Suggested algorithm for the investigation of suspected pulmonary hypertension. [5]



“Wild Poppies Near Argenteuil”, oil on canvas, 1873, Claude Monet.

“....The warm wind blows gently and the red poppies dance. The trenches have vanished long under the plow. No gas, no barbed wire, no guns firing now....”

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