Pulmonary Arterial Hypertension

Prof Anne Keogh
Cardiologist

St Vincents & Mater Health
Sydney

CONTENTS

CONTENTS

1 Normal function of the heart and lungs

1.1 The Cardiopulmonary Circulation

The cardiopulmonary (heart-lung) circulation is the flow of blood from the heart (cardio) to the lungs (pulmonary) via the pulmonary artery and then back to the heart, via the pulmonary veins.

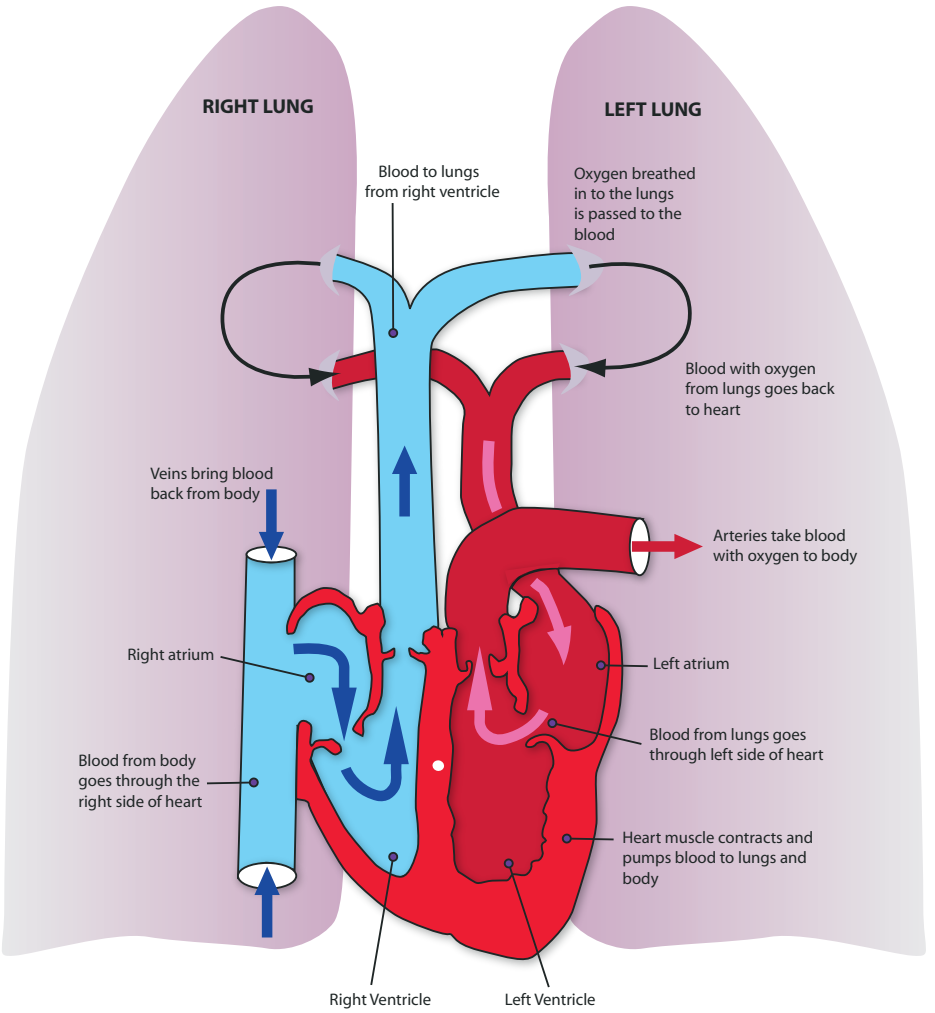

Fig 1. Normal Blood Flow of Heart and Lungs

1.2 The Heart

The heart is a muscular pump consisting of four chambers: the right and left atria and right and left ventricles. The right atrium receives blood from the entire body via two large veins known as the superior and inferior vena cavae. This blood has already had oxygen removed; and this blood is blue. From the right atrium, the deoxygenated blood passes through the tricuspid valve and enters the thin-walled right ventricle where it is then pumped into the pulmonary artery. This artery takes the deoxygenated blood into the lungs, where oxygen is added. The newly oxygenated blood passes through the 4 pulmonary veins into the left side of the heart - left atrium, left ventricle, then out through the aorta to the upper (head, arms) and lower body (kidneys, liver, legs) .

Interestingly, the heart does not derive its oxygen from the blood that flows through it. Instead, the heart has its own blood supply on the outside of the heart. There are three main arteries that branch off from the aorta i.e. the left anterior descending artery, circumflex artery and right coronary artery. These coronary arteries form the coronary circulation on the surface of the heart and then branch out further within the heart muscle (see Figure 2). These are the arteries which if blocked by cholesterol, fat etc, can cause a heart attack (myocardial infarct). However, in pulmonary hypertension, these arteries are usually normal.

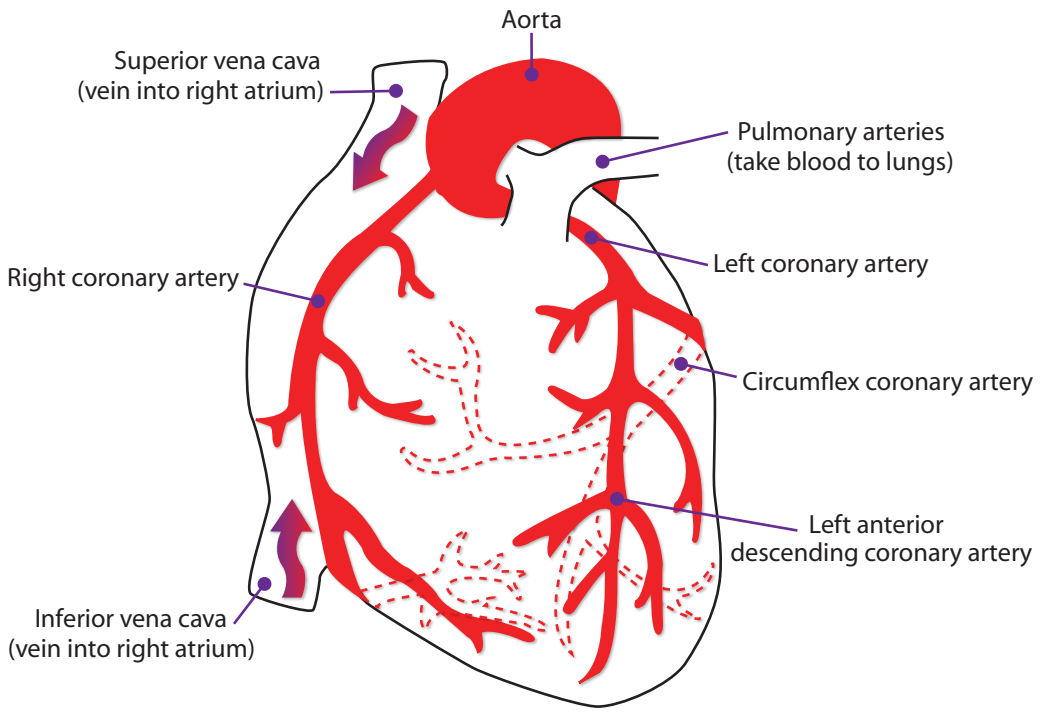

Fig 2. Coronary Arteries

1.3 The Lungs

The walls of the large part of the pulmonary artery are elastic and its elastic recoil propels blood into the lungs. When the pulmonary artery enters the lung, it branches out like a tree and the walls of the smaller branches contain muscle. Healthy children and adults have small amounts of muscle in their pulmonary arteries which are usually dilated (relaxed and open). In patients with pulmonary arterial hypertension, the walls cannot relax due to the increase in smooth muscle and scar tissue. These changes due to pulmonary arterial hypertension can now be partially reversed by medications (see page 17).

The main role of the lung is to restore oxygen in the blood. This takes place in the alveoli (air sacs) when you breathe in (see Figure below). The pulmonary veins then take the oxygenated blood into the left atrium. The blood then enters the left ventricle which has the greatest amount of muscle of all four chambers of the heart. The left ventricle has the important job of pumping blood into the aorta which delivers it to the entire body.

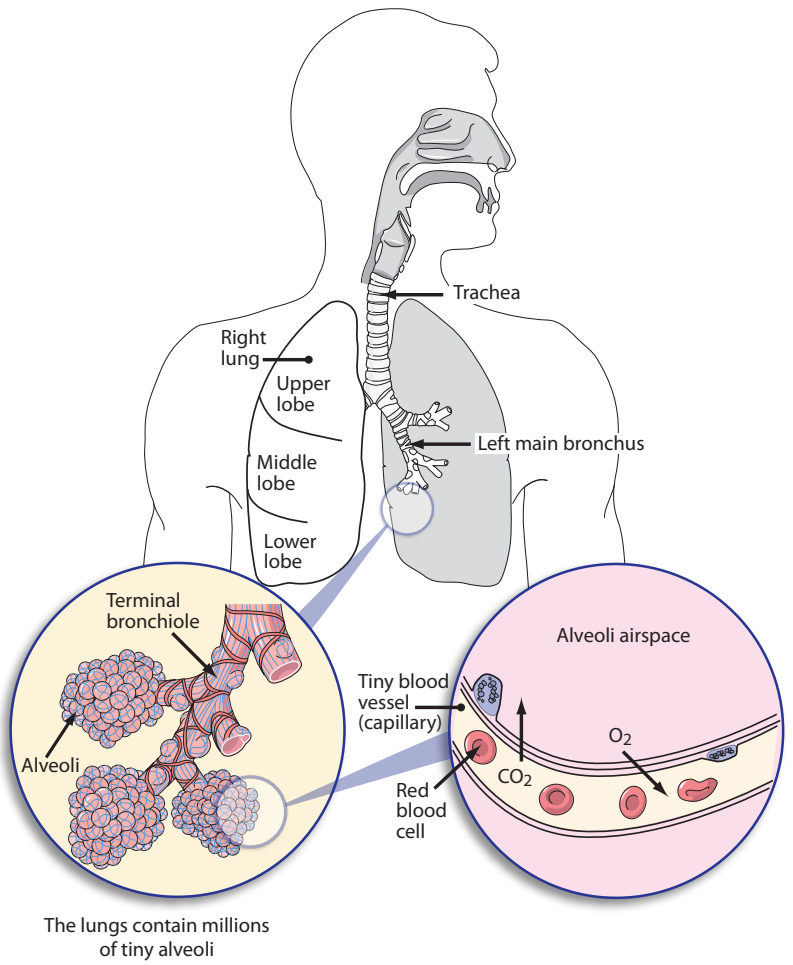

Fig 3. The Lungs Showing Alveoli

2 The development of pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) can develop out of the blue (idiopathic, which means no known cause) or may be genetically inherited (familial), and both forms are called Primary PAH. Alternatively, PAH may develop secondary to other diseases or conditions such as scleroderma, systemic lupus erythematosus (SLE), sleep apnea or thromboemboli (clots to the lungs), some types of congenital heart disease, liver disease and other causes.

In all cases, people with PAH have an increase in blood pressure in the pulmonary artery above normal. Normal mean (average) pulmonary artery pressure is below 25 mmHg at rest and below 35 mmHg during exercise. In general terms PAH is graded according to the mean pressure: mild (25-45 mmHg), moderate (45-65 mmHg) and severe (above 65 mmHg).

The real problem is not just the pressure, but that the right ventricle must pump against the higher resistance - pulmonary vascular resistance (PVR).

What causes PAH? The most widely accepted hypothesis is that the endothelial cells, lining all blood vessels, become damaged or dysfunctional. This results in an imbalance in the substances produced by the endothelium that cause constriction (tightening via endothelin-1, angiotensin II, thromboxanes) or dilation (relaxation via nitric oxide and prostacyclin). In most patients with PAH, the relaxing factors are decreased and the constriction factors are elevated which increases the pressure and resistance within the pulmonary arteries.

In addition there is also an increase in the muscle in the walls of these vessels. Connective tissue proteins (scar tissue) are deposited around the pulmonary vessels and in time they become stiff and can no longer dilate (relax, open up).

As the pressure in the pulmonary artery increases, the right ventricle must pump harder to force blood into the lungs. In order to do this the right ventricle grows more muscle. However this muscle requires a greater blood supply from the coronary circulation in order to function and this may cause chest pain or chest tightness. Eventually the right ventricle loses its ability to function and starts to fail (right heart failure). Signs of right heart failure are swelling in the ankles, pulsing in the jugular vein in the neck, a swollen liver, nausea and water (ascites or fluid retention) in the abdomen. There are several types of medication that can treat heart failure and these are summarised on pages 14 and 17.

2.1 Idiopathic pulmonary arterial hypertension

In Australia, idiopathic pulmonary arterial hypertension (iPAH) is a rare condition affecting 30 people in every million. IPAH can develop at any age and in both men and women. There is also a genetic component to iPAH and 10-25% of cases are familial (inherited). Family members may be advised to undergo screening for the disease with an echo and should especially be aware to watch for breathlessness.

Since there may be no symptoms during the early stages of iPAH, the disease is difficult to diagnose early. The most common symptom is dyspnea (shortness of breath) after physical exertion. Patients often mistakenly attribute this to lack of exercise, lack of fitness, obesity or smoking or 'just getting older'.

As a result, the period between onset of breathlessness and diagnosis may be as long as 2 years. In Australia, this time to diagnosis has dramatically decreased due to the growing awareness of PAH. Other symptoms of iPAH are fatigue, dizziness, palpitations, dry cough and angina - chest pain during exercise and breathlessness bending over. Fainting spells with coughing or fainting for no reason, represent quite advanced symptoms.

2.2 Secondary pulmonary arterial hypertension

As mentioned previously, PAH can also develop as a result of other diseases or disorders. Some of the more common examples of secondary PAH will be described in greater detail in this section. PAH symptoms can sometimes regress if the initial disease is treated in a timely manner. For example, surgery for congenital heart disease may prevent PAH developing in children who are born with a hole in the heart.

• *Scleroderma*

Scleroderma (skleros = hard, derma = skin) is an autoimmune disease affecting the connective tissue which supports blood vessels and other organs such as the skin and muscles. Diagnosis can be difficult as it may overlap with conditions such as rheumatoid arthritis and SLE (systemic lupus erythematosus). Since about 15% of patients with scleroderma develop PAH and they need to have yearly echocardiograms or respiratory function tests to screen for the disease. Common symptoms include lack of energy or fatigue, muscle aches and the CREST syndrome. CREST refers to **C**alcium deposits in finger tips, **R**aynaud's disease (red, white and blue fingers in the cold), **E**sophageal acid reflux, **S**cleroderma (puffy, thick fingers) and **T**elangiectases (tiny capillary outbursts called "spider nevi").

• *Systemic Lupus Erythematosus*

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease where the body is attacked by its own defence mechanisms. The disease is predominant in women between the ages of 10 and 50 years. Apart from the heart and lungs, SLE may also affect the muscles, kidneys, brain and the skin.

The symptoms of SLE vary considerably and depend on the organ or system affected. For example symptoms may range from fever, fatigue, nausea, low blood counts and rash, to seizures and psychosis. If PAH develops, however, the pulmonary hypertension responds very well to treatment and may return to normal.

• *Pulmonary Embolism & Chronic Thromboembolic Pulmonary Hypertension*

Emboli (moving blood clots) mainly originate from thrombi (clots) developing in the leg (after inactivity, an operation or after flying) or in the pelvic veins, but can also occur because of an inherent tendency for the persons blood to thicken. These emboli may then cause blockages of pulmonary arteries as the clots lodge in the lung artery branches and blood can no longer pass easily through the lungs to be oxygenated. Several pulmonary emboli are required to increase the resistance and pressure within small pulmonary arteries, resulting in PAH. A single pulmonary embolic event may not necessarily produce any symptoms. Patients with chronic thromboembolic PAH, may experience chest pain, breathlessness and fatigue – the same symptoms as idiopathic pulmonary arterial hypertension. Sometimes there is a family history of this condition.

• *Congenital heart disease and Eisenmenger's syndrome*

The most common types of congenital heart disease that result in PAH include those where blood is shunted to the right ventricle. This can occur via a hole in the wall/septum, which divides the two ventricles (ventricular septal defect) or the two atria (atrial septal defect). The increase in blood in the right atrium or ventricle is then forced into the pulmonary artery, which may cause damage to the endothelium lining cells which overproduce substances that constrict the pulmonary arteries thus causing PAH.

Other patients with PAH due to such events include those with patent ductus arteriosus (PDA), truncus arteriosus and transposition of the great arteries (TGA). In most cases, the PAH regresses if the congenital abnormality is corrected surgically at an early age and early stage of PAH. When PAH is more advanced, there may be changes in the structure of the blood vessels which might become irreversible if medication is not used.

• *Sleep Apnea*

Sleep apnea is repetitive and prolonged cessation or stopping of breathing whilst sleeping and may be accompanied by snoring. This causes a temporary decrease in the oxygen available for delivery to the brain and the rest of the body. People with this condition often feel exhausted waking from sleep and find it difficult to concentrate during the day.

The manner in which sleep apnea leads to PAH has generated considerable interest. Since oxygen is a natural dilator (opener) of arteries, the decrease in oxygen in the lungs causes constriction in the pulmonary vessels, eventually causing PAH. In those in whom sleep apnea develops because the back of the throat is unusually small, surgical correction can improve sleep apnea. Most cases of sleep apnea are due to a person being overweight or having a short neck, or both. Treatment with continuous positive air pressure (CPAP, see section 6.7) improves symptoms of PAH, restores normal breathing patterns during sleep and improves the restful value of sleep.

• *Other causes of pulmonary arterial hypertension*

Pulmonary arterial hypertension (PAH) can also develop as a result of other rare conditions. These include:

1. Portal hypertension (high blood pressure in the liver circulation)
2. HIV (AIDS)
3. drugs - diet pills such as dexfenfluramine, hallucinogenic agents such as 'euphoria' or methamphetamine ('ice') , St Johns Wort (Tiptons Weed, used for minor depression)
4. Lung Diseases including Chronic Obstructive Pulmonary Disease (COPD), Pulmonary Fibrosis.
5. Schistosomiasis (bilharzia), Sickle Cell Anemia and myeloproliferative blood disorders.

Symptoms

3 Symptoms

The symptoms of PAH increase with disease severity and are often accompanied by symptoms of heart failure which develops in some patients with PAH. Common symptoms include:

	Symptoms	Medical word
1.	Weakness	fatigue lethargy
2.	Shortness of breath	dyspnea
3.	Dizzy spells / fainting	syncope
4.	Swelling of the legs or ankles	edema
5.	Blue lips, skin or fingernails	cyanosis
6.	Chest pain	angina
7.	Racing heart beat/pulse	palpitations, (tachycardia, atrial flutter or fibrillation)

Functional Classification

4 Functional Classification

A functional classification system has been developed by the New York Heart Association (NYHA) - also known as the World Health Organisation functional classification (WHO) to grade the symptoms of PAH into the following groups:

Class I: Patients with no symptoms of any kind and for whom ordinary physical activity does not cause fatigue, palpitation, dyspnea or angina i.e. normal.

Class II: Patients who are comfortable at rest but have symptoms with ordinary physical activity e.g. gardening, walking up steps, carrying 10 kgs.

Class III: Patients who are comfortable at rest but have symptoms with less than ordinary effort e.g. walking around the house.

Class IV: Patients who have symptoms at rest and there is no effort which is comfortable. The person may be restricted to bed.

5 Diagnosis

5.1 Electrocardiogram

The electrocardiogram (ECG) is a print-out of the electrical activity of the heart. This may be recorded at rest or during exercise e.g. walking on a treadmill. An abnormal ECG may be indicative of poor cardiac function and can detect if the patient has had a heart attack which has gone unnoticed (e.g. silent heart attack). It can also detect if the right ventricle is becoming more muscular in order to increase the amount of blood pumped into the lungs, and detect rhythm disturbances.

5.2 Echocardiogram

The echocardiogram uses sound waves to examine the structure of the heart by placing a microphone-like device on the patients chest. The sound waves that are sent into the heart are reflected back to form a moving image of the beating heart. This test allows the doctor to measure the thickness of the heart muscle and to some extent, the pressure in the pulmonary arteries and any leaking of the tricuspid valve.

Generally, in patients with PAH, the right heart is enlarged while the left heart is normal or even squashed by the right ventricle and reduced in size. Apart from diagnosis, the echocardiogram is useful in monitoring the response to treatment. The limitation is that it can only measure pressure but **not the resistance** in the pulmonary arteries.

5.3 Pulmonary function tests (lung function tests, respiratory function tests)

These tests examine the function of the lungs. The patient's nose is clipped while they are asked to breathe in and out of a mouthpiece. Measurements of lung volume (amount of air in the lungs) and air flow are recorded.

In patients with PAH, there is a restriction to gas movement (DLCO) through the small air sacs within the lungs. In scleroderma, scar tissue or fibrosis in the lungs may also lead to a restricted amount of lung being available for oxygen flow.

5.4 Right-heart catheterisation

Catheterisation is performed by a cardiologist. A thin plastic tube (catheter) is inserted through a vein in the neck, arm or leg (under local anaesthetic) and is then gently guided into the right ventricle and pulmonary artery. The patient is awake during the procedure and discomfort is minimal.

The catheter provides the key information as to the exact pressures within the right ventricle and pulmonary artery. The ability of the heart to pump blood into the pulmonary artery (cardiac output) and the presence of unsuspected holes in the heart can also be established. This procedure is the only way doctors can precisely and definitely make the diagnosis of PAH.

The most important measurement is NOT the pulmonary artery pressure but the pulmonary vascular resistance (PVR). Normal PVR is below 3 Wood Units or below 240 dyne/cm/sec-5. The PVR should fall with successful treatment.

5.5 Six -minute walk test

This test is an easy way to determine exercise performance. The patient is asked to walk up and down a corridor for 6 minutes and the distance walked is measured. The amount of oxygen in the blood (oxygen saturation) may also be recorded. The patient may be asked to fill in a questionnaire to describe their breathlessness (dyspnea) before and after the six-minute walk.

To calculate your expected six minute walk distance, insert your height in metres (eg. 1.68m) and weight in Kilograms (eg 76kg) and do the mathematics!!

YOUR EXPECTED 6 MINUTE WALK DISTANCE IN METRES

Male	**757 x Ht - 5.02 x Age - 1.76 x Wt -309**	**=**	
Female	**211 x Ht - 5.78 x Age - 2.29 x Wt + 667**	**=**	

5.6 Pulmonary angiogram

An angiogram provides a picture of your pulmonary arteries which can help to determine to what degree they are blocked. This procedure will exclude the presence of pulmonary hypertension due to emboli. These images may be generated by a computer and a tunnel/tube-like scanner (CT-angiogram) or via x-ray type film ("cut film" angiogram). In both cases an iodine dye is injected into the bloodstream and outlines the arteries including the pulmonary artery.

5.7 Virtual CT Coronary Angiogram

Patients may require a coronary angiogram i.e. study of the blood vessels running on the outside of the heart. This is a five minute CT scan which takes the place of having an in-patient coronary angiogram. It involves an injection of contrast (iodine) and then the CT scan. The test is performed as an out-patient and its purpose is to detect blockages in the arteries to the heart and also measure calcium in the walls of the arteries.

6 Treatment

Once PAH has been diagnosed, treatment may begin. Presently there is no cure for PAH but one can be quite well and healthy using the right combination of medications. While most patients under treatment for PAH lead a fairly normal life, there are some whose PAH is so advanced that they do not respond to therapy.

6.1 Conventional Medication

The conventional medications prescribed for the management of PAH are shown on page 14. The brand name (marketing name) and the actual drug name (generic name) are given, along with the class of drugs to which they belong and their main side effects.

One of the therapies is calcium channel blockers but only 5% of patients respond long term. These drugs are able to relax the wall of the pulmonary artery and other arteries in the body and decrease pressure.

6.2 Warfarin

The other main therapy is warfarin, which thins the blood. Patients with iPAH taking warfarin have been shown to live longer, but this is not the case with other causes of PAH. Warfarin is recommended in all patients with iPAH or thromboembolic PAH, except those who have a history of serious bleeding. The INR target will differ depending on the cause of PAH in an individual.

There is no evidence that aspirin is helpful in PAH patients and it is not a warfarin substitute.

Warfarin requires regular blood tests and can interact with many other drugs and foods including vitamin K containing leafy green vegtables, antibiotics and some herbal medications. The packet insert contains an itemised list (see page 20).

6.3 Conventional medications for pulmonary arterial hypertension

Drug class	Drug name	Generic brands	Effects of drug	Side Effects
Anticoagulant	Warfarin	Coumadin Marevan	Prevents blood clots	Bruising, bleeding gums, rash, hair loss, nose bleeds
Calcium channel antagonists (CCB)	Verapamil Diltiazem Amlodipine Nifedipine	Isoptin, Cardizem, Norvasc, Adalat	Relaxes the walls of the lung blood vessels	Ankle swelling, flushing, headaches, dizziness
Diuretics	Frusemide Bumetamide Amiloride Spironolactone	Lasix, Urex Burex Midamor, Kaluril Aldactone	Decrease swelling via loss of fluid	Dry mouth, dry skin, rashes, cramping (at high doses) lowered potassium and magnesium levels Breast development (spironolactone)
Inotropic agents	Digoxin	Lanoxin	Stimulates contraction of the heart	Side effects are rare except if digoxin has built up in the blood stream. Nausea, vomiting, loss of appetite, diarrhea, yellow-green halo vision.
Nitrates	Glyceryl-trinitrate Isosorbide dinitrate	Angine, Nitrospray Isordil, Imdur, Nitrobid, Transiderm patch	Vasodilators (increase blood flow)	Headaches (temporary), Dizziness (on standing), Low blood pressure.
ACEI	Captopril Enalapril Lisinopril Perindopril	Capoten Renitec Prinivil Coversyl	Inhibit vasoconstriction (ie. contraction of blood vessels) and growth of muscle in vessels and heart	Dizziness, dry cough, rash, high potassium levels, metallic taste in mouth
ARBs Angiotensin Receptor Blockers	Irbesartan Candesartan Telmisartan	Avapro, Karvea Atacand Micardis	Vasodilator (increases blood flow) and stops excessive growth of muscle in the heart and blood vessels	Dizziness, same side effects to ACEI except for the cough
Beta Blocker	Atenolol Metoprolol Bisoprolol Carvedilol	Noten Betaloc, Topol Bicor Dilatrend	Slows heart rate, strengthens the left ventricle	Slow heart rate, low blood pressure, fatigue, dizziness, worsening heart failure, diabetes, asthma, leg pains during exercise, rash

6.4 PAH Drugs

A variety of medications have been approved by the PBS for the treatment of PAH (and some are awaiting future approval in Australia). Description see page 17.

Prostacyclins (Treprostinil, Epoprostenol, Iloprost)

Prostacyclin is a vasodilator substance that is produced by the endothelial cells that line all blood vessels. This substance keeps arteries dilated (open) so blood can reach tissues. Prostacyclin production is deficient in the lungs of patients with PAH. This would tend to keep the pulmonary arteries constricted which increases the blood pressure within the arteries. Therefore there is less blood passing through the lungs at any given time to be oxygenated.

Flolan® (intravenous Epoprostenol) is a synthetic prostacyclin which mimics the effect of natural prostacyclin in the body. Iloprost (inhaled Ventavis®) is designed to act like prostacyclin. Both these drugs are available on the PBS. The main action of this class of drug is to increase blood flow and decrease pulmonary artery pressure.

Iloprost

Ventavis® (iloprost) is inhaled 5-9 times a day and is also approved for PAH treatment. The drug is delivered via a special nebuliser called the I-neb® which is provided, free of charge, to patients using iloprost. Iloprost works best when used in combination with other PAH therapies.

Endothelin Receptor Antagonists

Tracleer® (bosentan) is the first member of a class of drugs called endothelin receptor antagonists (ERAs). ERAs blocks the actions of a substance called endothelin-1 (ET-1). ET-1 is normally produced by the endothelium in small amounts and causes the constriction of blood vessels and the growth of smooth muscle. Studies spanning the last 10 years or so have established that ET-1 is elevated in the lungs of patients with PAH. This may be due to an increase in its formation or a decrease in its breakdown by the lung. ERAs (see page 17) prevent prolonged constriction of the pulmonary arteries and decrease the blood pressure within these arteries and reducing symptoms of PAH. In iPAH and PAH due to scleroderma or SLE, ERAs reduce pulmonary artery pressure and improve exercise capacity and wellbeing, stabilise the disease and prolong survival. In many patients, ERAs may even reverse the changes in the structure of blood vessels in the lung. This restores free blood flow and allows the patient to breath more easily. The result is an increase in the amount of oxygen in the blood that can be used by the body. Most patients respond favourably to ERAs and side effects are relatively few.

Sildenafil, Tadalafil

Revatio® or Viagra® (sildenafil) and Cialis® (tadalafil) are other treatments for PAH. They have the ability to dilate blood vessels which is the main mode of action when used for the treatment of erectile dysfunction. Sildenafil inhibits the enzyme that degrades the natural vasodilator, nitric oxide. Patients with PAH have smaller amounts of nitric oxide produced by their pulmonary arteries. This results in greater constriction of blood vessels and consequently increased pulmonary artery

pressure. Sildenafil decreases this elevated pulmonary artery pressure and reduces the symptoms associated with PAH. The side effects of sildenafil are shown on page 17. **Sildenafil cannot be taken with nitrates**. Sildenafil is also available as Viagra®. Viagra tablets come in (25mg, 50mg or 100mg) tablets while Revatio comes in 20, 40 or 80mg tablets.

Viagra® does not cause erections itself, only if the man is aroused.

L-arginine

L-arginine is a semi-essential amino acid necessary for the maintenance of blood vessel function. Specifically it is able to dilate all blood vessels, keeping them open thus allowing a steady flow of blood. L-arginine can be derived from foods (see page 18) or may be taken in tablet or powder form. These are available from chemists and health food shops. It is important to know that just changing your diet according to the food pyramid can make a difference to your PAH.

6.5 Heart lung transplant

Heart lung transplantation is reserved for patients with severe PAH, when organs are extensively diseased. Generally this is not performed in those over 50 years of age.

6.6 Oxygen at home

Patients with PAH may require oxygen at home, depending on the severity of their symptoms. Oxygen may improve symptoms, as it is able to dilate pulmonary arteries, even if it is just used at night at home.

6.7 Oxygen when flying

Commercial airplanes are pressurised, but nonetheless, the amount of oxygen in the cabin is lower than on the ground. Some PAH patients may be uncomfortable flying, unless oxygen is used in-flight. If there is any concern or uncertainty, a high altitude test can be performed, simulating the lower oxygen in a plane. This test will determine if oxygen is required during the flight.

6.8 CPAP

Sleep apnea (stopping breathing, snoring, frequent waking during the night) can contribute to PAH. It can be treated with continuous positive airway pressure (CPAP). CPAP is delivered by a machine through a mask worn at night. This prevents the air passages collapsing and blocking off which prevents snoring and improves breathing.

New Drugs

Brand name	Generic name	Delivery	Effects of drug	Side Effects
Flolan® Remodulin® Beraprost® Ventavis®	Prostacyclin Treprostinil Beraprost Iloprost	Central line/ intravenous Subcutaneous infusion Tablet / oral Inhalation / intravenous	Dilates blood vessels	Headache, nausea, diarrhea, flushing, hypotension, injection site pain (treprostinil), jaw pain
Tracleer® Thelin® Volubris®	Bosentan Sitaxentan Ambrisentan	Tablet / oral Tablet / oral Tablet / oral	Vasodilator (increases blood flow) and stops excessive growth of muscle in the heart and blood vessels	Headache, stuffy nose, flushing, abnormal liver function, edema, low blood pressure, palpitations, fatigue, itching
Viagra® Revatio® Cialis®	Sildenafil Tadalafil	Tablet / oral Tablet / oral	Dilates blood vessels via prolonging the action of nitric oxide (by inhibiting its breakdown). **Cannot be taken with nitrates ie arginine, nitrospray, imdur, nicorandil, nitrate patches.**	Headache, flushing, indigestion, nasal congestion, zig- zag blue vision (at high doses), diarrhea, dizziness, rash, rarely loss of vision in one eye.
L-arginine	L-arginine	Tablet or powder / oral	Dilates blood vessels	Diarrhea, nausea, tastes bad

Foods Rich in L-Arginine

Food Group	Food (per 100gm serving)	*L-Arginine content (grams per 100gm of food)
Dairy	Milk	0.13
	Chedder Cheese	0.90
	Eggs	0.89
Meat	Lamb	1.39
	Veal	1.54
	Beef	1.54
	Chicken	1.39
	Pork	1.53
	Tuna	1.25
	Sardines	1.31
	Salmon	1.33
Breads and Cereals	White Bread	0.31
	Wholemeal bread	0.36
	Wheat flour	0.43
	Wholegrain wheat	0.62
	Oats	0.87
Beans	Lima beans	1.39
	Chickpeas	1.48
	Lentils	2.24
	Soya beans	2.36
Nuts	Macadamias	0.99
	Cashews	1.98
	Hazelnuts	2.03
	Walnuts	2.09
	Brazil nuts	2.12
	Almonds	2.75
	Peanuts	3.46

6.9 Warfarin and interactions

Warfarin is taken in order to prevent blood clots forming in the blood vessels. Vitamin K has an important role in the formation of blood clots. A high intake of vitamin K rich foods can interfere with the effectiveness of warfarin. It is important to keep your vitamin K intake from food constant from day to day to balance your prescribed dose of warfarin.

Here are some tips on how to achieve a regular intake of vitamin K

1. **Have regular meals based on the food pyramid**
2. **Don't skip meals, crash diet or binge eat**
3. **Choose only one serving each day of the following, as these foods are high in vitamin K:**

Asparagus	1/2 cup
Alfalfa	2 tablespoons
Broccoli	1/2 cup
Brussel sprouts	5
Cabbage	1/2 cup
Cauliflower	1 floret
Coleslaw	1 cup
Lettuce	2-3 leaves
Liver	100g
Soya beans	1/2 cup
Spinach	1/2 cup
Green Tea	1 cup

Canola and Soya bean oil are high in vitamin K and olive oil has a medium content of vitamin K. It is better to use either sunflower, almond, walnut, sesame seed, peanut or corn oil.

4. **Alcohol should be restricted to no more than 2 standard drinks per day.**

   2 standard drinks = 2 middies of beer (570mls) = 200mls of wine = 2 nips (30mls) of spirits

5. **Avoid vitamin supplements with vitamin K, read labels carefully. Large amounts of vitamin C (more that 5 grams per day) and vitamin E greater that 400 units per day affect warfarin.**

7 Managing your pulmonary arterial hypertension

Aside from taking medications, there are other ways to can improve your wellbeing. A combination of exercise, a healthy diet and not smoking are some of the best measures in improving the health of your heart and lungs.

7.1 Exercise

Exercise is encouraged, simply going for a daily walk, and is beneficial for patients with PAH, as you will now be able to perform tasks that require physical activity. Doctors and physiotherapists can assist patients with finding the exercise that best suits their capabilities. It is important to discuss the correct exercise regimen with your PAH team. Medicare provides 5 reimbursed treatments per year.

7.2 Sexual activity

Patients with PAH may find that sexual activity causes breathlessness and chest pain. The well partner may need to take the active role.

7.3 Diet and fluids

Salt intake should be restricted because this may aggravate symptoms. Salt can be added to the cooking but not at the table.

For weight and cholesterol control, fats and oils (dairy, butter and margarine) should be limited or not used at all. Unsaturated fats found in cheese and red meat can increase cholesterol in the blood leading to blockages of various arteries in the body, including the coronary arteries.

Take a diet full of vegetables, cereals, pasta, fruit, soy and bread but avoid dairy, cheese and most spreads. If oil is to be used, choose olive oil, or if spreads are used, choose olive or canola oil. Following the food pyramid will benefit your health (page 21).

Some patients will need to restrict their fluid intake.

7.4 L-arginine

In patients with PAH, a diet rich in the amino acid L-arginine, is thought to improve some of the symptoms of PAH. L-arginine is the substance that forms the vasodilator nitric oxide which dilates blood vessels. In addition, L-arginine is key to the synthesis of tissue proteins such as collagen and elastin that provide structural support for organs in the body.

Foods rich in L-arginine are shown on page 18. Fruits and vegetables should be consumed liberally (except by diabetics) as they are a rich source of vitamins and antioxidants. Ideally, aim for a total l-arginine intake of 3-6 grams per day. This may require supplements of L-arginine in capsule or powder form (1 gram taken 3 times a day).

THE HEALTHY EATING PYRAMID

Department of Nutrition, Harvard School of Public Health

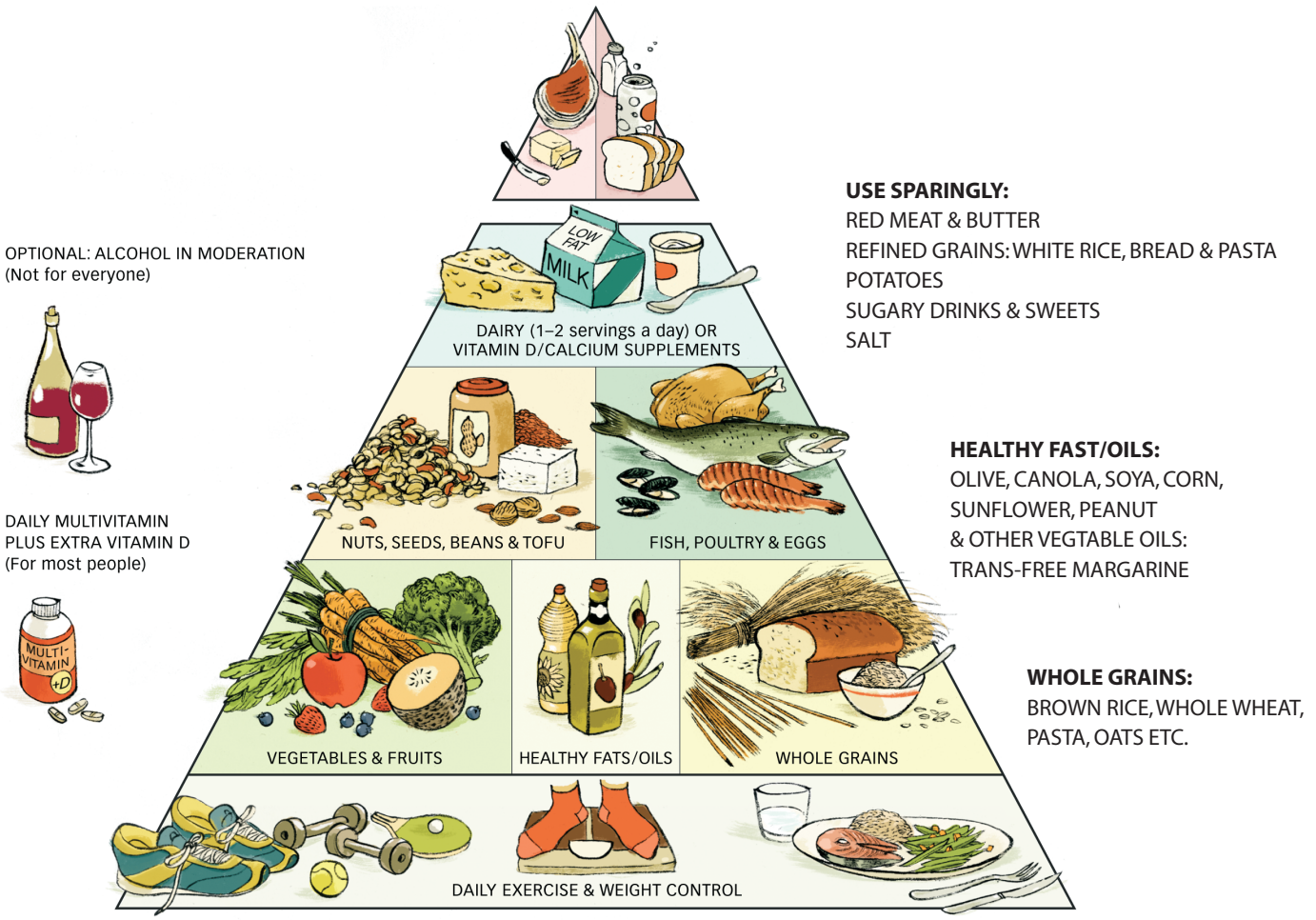

Figure 4 Decrease your intake of food at the top of the pyramid and increase your intake of food at the bottom of the pyramid

For more information about the Healthy Eating Pyramid

WWW.THE NUTRITIONSOURCE.ORG

7.5 Herbs and naturopathy

The use of herbs, naturopathy and Chinese medicines may also alleviate symptoms of PAH. For example, turmeric is thought to reduce pulmonary artery pressure (no solid proof). Coenzyme Q10 and selenium supplements may also be beneficial and are safe. However, there some natural therapies that contain substances which can interact with your medications, (eg Coenzyme Q10 and warfarin) so consult your doctor before starting these therapies.

7.6 Body weight

By checking weight against height, you can determine whether you are overweight (or underweight), compared to average measurements. To calculate your Body Mass index (BMI) divide your weight in kilograms by your square of height in metres (i.e. height multiplied by height). This is summarised by the formula:

$$BMI = \frac{\text{Weight (kg)}}{\text{Height}^2 \text{ (m)}}$$

BMI	10 - 20:	Underweight
	20 - 25:	Healthy
	25 - 30:	Overweight
	30 - 40:	Obese
	40 - 60:	Extremely obese

7.7 Smoking

Patients with PAH must not smoke. Smoking causes blockages in the coronary arteries. This makes the heart work harder by increasing the blood pressure and the heart rate. In addition, smoking causes further obstruction of the pulmonary arteries and impairs lung function, which are both compromised in those with PAH. It also worsens Raynaud's and scleroderma.

7.8 Alcohol

Alcohol can reduce the hearts pumping ability and also increases the effects of Warfarin. Intake should be discussed with the doctor.

7.9 Vaccines and influenza

A cold or influenza (flu) can cause serious deterioration in the symptoms of PAH. We advise FluVaxTM before the beginning of each winter and PneumoVaxTM every five years. If you do get a chest infection (bronchitis or pneumonia), antibiotics may need to be given for weeks or many months (rather than days or weeks). Similarly, seek attention early for abcessed teeth, urine infections or other infections.

Internet websites provide information about PAH and treatments. Some of these sites also offer support groups for patients with PAH.

The internet does not always give good quality or correct information. Please bring up any issues with your doctor.

8 INTERNET SITES ON PULMONARY HYPERTENSION

NAME	WEBSITE/ADDRESS	INFORMATION PROVIDED
phnsw	www.phnsw.org.au	Provides locally focused information and support
Pulmonary Hypertension Association (USA)	www.phassociation.org	Provides international updates on pulmonary hypertension information and research
Pulmonary Hypertension Association Australia (PHA)	www.phaaustralia.com.au	Provides national information and support
Scleroderma from A-Z	www.sclero.org	Information about this disease and links to other sites
Lupus Association of NSW Inc.	www.lupusnsw.org.au	Located in Ryde, NSW, provides information about the disease, symptoms and treatments

9 Clinical Trials

The Pulmonary Hypertension Clinic at St Vincent's Hospital has had a special interest in PAH since the late 1980's and has been at the forefront of recent medical breakthroughs. This has been achieved by involvement in a wide range of international clinical trials. These important studies are often the only way that patients can access the newest treatments for PAH years ahead of time.
There are two types of trials. The first is **double-blind,** where patients on usual therapy receive either the new drug or 'placebo' (inactive tablet) on top of the existing therapy. The allocation is random and neither the doctor, nurses nor patient know who is in which group until the trial is completed. These trials usually run for three months. Interestingly, even the placebo group tends to fare better than those who do not take part in trials. This is because of the tightly scheduled follow-ups and testing that are mandatory for every participant in the trial. Once the trial is completed, free medications are offered to all patients ongoing, irrespective of whether they received placebo or active drug during the trial.

The second type of trial is an **open label trial** and everyone participating receives study drug. This is also called a compassionate access trial. In some open label trials, free drug is provided until it becomes PBS reimbursed (Pharmaceutical Benefits System) in Australia.

10 Tip Sheet

Patient Educational Material Written by Patients

1. Do stairs daunt you? Turn around and go up backwards. It may look strange but it's easier to push than to pull. Do not stumble! This also works when you must go up a hill or incline.
2. I often feel dizzy when I first get out of bed. I have found that it helps if I do leg-lifts before I get up, then I get up slowly and sit on the edge of the bed for a few minutes. I wiggle my toes and swing my legs. Then stand up while keeping my eyes straight ahead.
3. I keep inexpensive, light weight camp chairs strategically placed around the house, garage, and porch to sit upon instead of bending when I have to do work close to the floor or ground.
4 When you feel really tired, it is imperative to slow down. When your heart beats too fast, your pulse races, or you can't seem to get enough air, stop right then and sit down.
5. When short of breath, lift arms slightly from your sides to allow more room for your chest to expand. You can take deeper breaths.
6. Although diet helps, exercise is the key to keeping down weight, but for many of us, true work-outs are out of the question. I have found that I can do some exercising in the swimming pool. Many of the things I cannot do out of the water, I can do in the pool.
7. Be organised. Know where everything is and keep thinking of ways to simplify tasks.
8. I always push a shopping cart around the store even if I don't have a thing to put in it because it gives me something to rest on.
9. If you have an electric bed, put the bed in the up position before putting on the bottom fitted sheet, then lower the bed and the sheet will tighten on its own.
10. Try wearing a hairstyle that can be washed , dried and brushed out. Avoid using a hair dryer or curling iron because holding your arms above your head takes a lot of energy.
11. For spot mopping push a soapy rag around the floor with your foot. This is great for those hard to reach places such as behind the toilet or under a table.

Occupational Therapy

1. Stay busy. Activities are not always of a physical nature. Live for today, but look ahead and plan things that you can do or create.
2. To help occupy time, I do couponing and refunding. It's amazing how much I can save and it is something that can be done while sitting down. I save even more by shopping on double coupon days and watching for sales. It is not unusual for me to save 1/3 to 1/2 of my total grocery bill.
3. I enjoy playing trivia contests with the radio stations. There is no cost involved. Prizes range from dinner at restaurants, amusement park tickets, and theatre tickets to gift certificates, citrus fruits, and concert tickets.

Tip Sheet

Prescriptions and Health Care

1. Write out all your prescription needs for a month's supply of medication. Submit these to five pharmacies (include a large volume discount store or Pharmacy Direct) telling them that you are price comparing. Many times you will find that you will get a lower price.
2. Research the cost of your prescribed drugs compared to the generic drug from your pharmacy (different pharmacies may use different generic brands).
   Talk with your physician about using the generic drugs
3. It is important that we follow the doctor's orders precisely when taking medications. He or she really can't be in charge of your well being if you are skipping doses or taking medications in an inappropriate manner. Some drug dosages need to be decreased slowly not abruptly. When a new medication is introduced, ask questions and be sure you understand what it is supposed to do and if there are any side-effects. In some cases, the doctor will have samples of new medications and can use them to see if they are helpful before you get a costly prescription filled.
4. If you don't wear medical identification bracelet, consider it.
5. If you have ankle swelling, keep them elevated when sitting for periods of time.
   Rotate ankles.
6. To help you remember questions to ask the doctor, keep a little notebook and jot things down as you think of them. Take the notebook on your next visit.
7. Something that is often overlooked, and shouldn't be is our health in general.
   We are naturally concerned with the foremost problem. But it is imperative that we remember other things can go wrong also. Don't forget your regular physical checks.

Products

1. Household- Various household products can irritate sensitive lung tissue and compromise oxygen. Chlorine and aerosol sprays irritate and sometimes are down right dangerous.

   Use with caution. Avoid using paints or thinners, pesticide or lawn care sprays, or flammable liquids which can cause many problems. Powders and products that produce or disturb dust should be used with utmost caution. Be aware of and avoid any toxins in your environment, including your neighbours lawn spraying service!
2. My complexion has become very pale since my diagnosis of PPH. I am also troubled by broken veins and bruises. I have found that using a sunless tanning product or UV light blocking foundation can mask these problems. I have tried various brands and find that the least expensive brands comparable to the more expensive brands.
3. Medical waste: Dispose of your medical wastes safely. Use sharps disposals units for needles. Ask your doctor or lab to dispose of full containers properly and safely.

   DO NOT THROW USED NEEDLES OR DRUGS IN YOUR REGULAR TRASH -
   take them to a pharmacy
4. Support recycling efforts. "Reduce re-use -recycle" anywhere you can. The less waste to dispose of, the cleaner and more beautiful our world will be.
5. Beware of the hidden sodium. There are many sources of sodium beside salt.

Holiday goodies, baked goods, dairy products, canned goods, powdered sauces, seasoning blends, condiments and processed meats can contain MSG, Sodium Citrate, Sodium,Benzoate or Sodium Phosphate. Baking powder and baking soda contain Sodium Bicarbonate. Tomatoes, celery and other fresh foods may contain comparatively high amounts of sodium naturally. Read labels and count every gram!

11 The Future

Pulmonary arterial hypertension (PAH) has gained significant recognition over the past decade due to the development of several new therapies. In fact, the availability of these therapies has already improved survival vastly. In some patients, we are seeing relative "cures", that is normalisation of pulmonary pressures on multiple drug therapies. For others, these therapies have allowed the deferral and in some cases, avoidance of heart lung transplantation. However, each patient will respond differently to therapies and the course of PAH varies in individuals.

This is a promising time for patients with PAH due to the rapid increase in therapies available. The specialised staff at the St Vincent's Hospital PAH clinic are committed to continuing advances in PAH treatment to improve the quality and the quantity of your life. We will be able to tell you all information about new drug trials.

Acknowledgements for this publication

Karen Brown
Carolyn Corrigan
Leonora Diaz
Julie Murray
Eimear O'Sullivan
Ross Pettersson
Annette Pidoux

NOTES