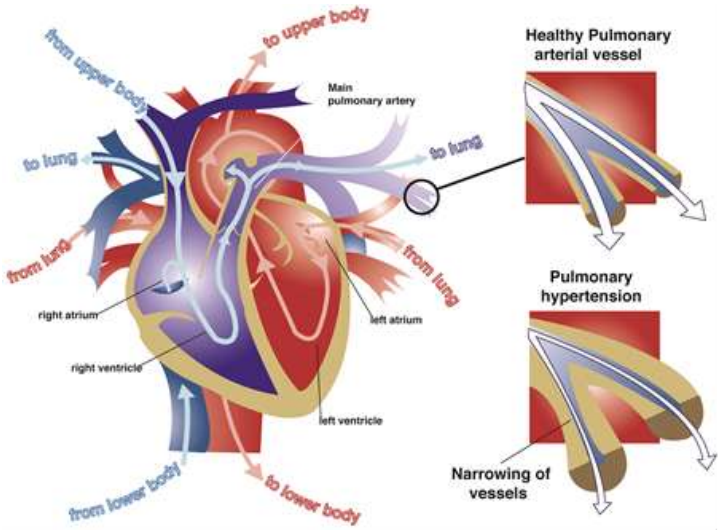
Dear All

Welcome to our mid-year ARRC newsletter for 2018. Amongst the spectrum of disturbances of immune function, autoimmunity is one of the more important causes of chronic illness, affecting around 5% of the population, and representing the third commonest chronic health challenge after cardiovascular disease and cancer. Autoimmunity (sometimes referred to as "unregulated mischief", or "immune confusion") may be generalised ("systemic") or organ-targeted. Examples of systemic autoimmune conditions, which may affect multiple parts of the body, include systemic lupus, Sjögren's and scleroderma; organ-specific autoimmunity is exemplified by thyroiditis, chronic urticaria and pernicious anaemia. Another form of organ-specific autoimmunity which our centre is involved in researching and managing is pulmonary artery hypertension, and this forms today's topic.

Pulmonary Artery Hypertension (PAH): An Overview

What is PAH? - Pulmonary artery hypertension (PAH) is diagnosed when medical tests reveal increased resistance to flow due to narrowing of the vessels running from the (right-side of the) heart to the lungs.



Blood goes to the lungs to pick up oxygen before being pumped through the body by the left-side of the heart, so PAH often presents with shortness of breath due to reduced oxygen levels in the blood. The normal number for pulmonary vessel resistance (PVR) is less than 3 ("Woods") units, and pulmonary artery pressure (PAP) is normally less than 15 (mm Hg). Values for PVR of more than 3, or PAP more than 20, are the defining feature of PAH (as long as left heart function [defined by a "wedge" (PAWP) pressure □ 15] is normal). Because the right-side of the heart is pumping against a greater load, this strains the heart, causing palpitations, fatigue and chest discomfort, and may cause right-heart failure, which shows itself by breathlessness and dizziness on exertion and ankle swelling (oedema).

What PAH Is Not - PAH is different to what is commonly referred to as "blood pressure" 0(elevated systemic blood pressure (SBP), or systemic hypertension (SHT)), which is a raised pressure in the vessels supplying blood to the body from the left-side of the heart through the aorta and its branches, as reflected by readings detected using the "blood pressure cuff".

PAP can also go up in people with lung disease, hypoxia, thromboembolism (clots), and left heart muscle or valve disease, which must be ruled out before PAH can be diagnosed.

What Causes PAH? - The reasons why PAH develops in some people are often unclear. PAH is not just due to muscle contraction in the vessel walls, but also reflects disturbed function of cells lining the inner vessel walls (endothelial cells), vessel narrowing due to cell proliferation and scar tissue formation, along with more general changes in immune function (inflammation) and clotting. When no clear cause is found for PAH, it is called “idiopathic”; other causes are listed in Table 1. Note that there may be a genetic component in some people (as reflected by PAH running in the family).

Table 1: Pulmonary Hypertension Classification	
Group 1 – “True PAH” **Idiopathic (IPAH), heritable, connective-tissue-disease associated**	**Group 2 PH – Due to left heart disease** **Group 3 PH – Due to lung disease / hypoxia** **Group 4 PH – Secondary to clots (Chronic thromboembolic PH = CTEPH)** **Group 5 PH – Miscellaneous (e.g. sarcoid)**

How is PAH Detected? - When suspected, echocardiography (“echo”) represents a sensitive and non-invasive tool to detect PAH: it involves the use of an ultrasound probe applied to the chest wall over the heart to detect heart pump function and evidence of leakiness of a right-heart valve (tricuspid regurgitation) commonly seen with PAH. In order to confirm the diagnosis of PAH, cardiological expert panels and government authorities advise that right heart catheterisation (“cardiac cath”) be performed, particularly when expensive

and potentially toxic treatments are being considered. This involves the direct measurement of heart pressure via a fine line introduced through the groin, arm or neck. The diagnostic workup always includes performance of a “six minute walk”, which measures the “six minute walk distance” (6MWD). This is the greatest distance you can walk in six minutes: distances less than 300m require particularly intensive treatment.

Symptoms Suggesting PAH - PAH should be considered whenever breathlessness or dizziness on exertion, palpitations, chest discomfort, swelling or unexplained fatigue occur. Breathlessness is often classified using the so-called “WHO Functional Classification”, which grades the impact of breathing limitation on everyday activities (see below).

WHO Functional Classification of Pulmonary Arterial Hypertension	
Class	**Description**
I	No limitation of usual physical activity; ordinary physical activity does not cause increased dyspnoea (breathlessness), fatigue, chest pain, or presyncope (dizziness).
II	Mild limitation of physical activity; no discomfort at rest, but normal physical activity causes increased dyspnoea (breathlessness), fatigue, chest pain, or presyncope (dizziness).
III	Marked limitation of physical activity; no discomfort at rest, but minimal ordinary activity causes increased dyspnoea (breathlessness), fatigue, chest pain, or presyncope (dizziness).
IV	Inability to perform any physical activity at rest and possible signs of right ventricular failure; dyspnoea (breathlessness), fatigue, or both may be present at rest, and symptoms are increased by almost any physical activity.

What Other Settings Should Prompt a Search for PAH? - PAH should be considered not only when symptoms such as breathlessness occur, but also it should be screened for in people recognised as being “at risk” for PAH, such as individuals with scleroderma, lupus, congenital heart disease and HIV.

Is PAH really autoimmune? - Immune disturbances do contribute to PAH, especially in the subset with connective-tissue diseases such as scleroderma (PAH prevalence =10%) and lupus (PAH prevalence=5%). Autoantibodies can often be detected, including ANA and targets such as anti-centromere (seen in limited scleroderma/”CREST”), Scl-70 (anti-topoisomerase I) and anti-RNA polymerase III; anti-endothelial cell antibodies (directed against vessel wall linings) can also be found. Some case reports exist of beneficial response of PAH to immune suppression, although this is controversial and not part of routine standard care. The coexistence of PAH with other autoimmune conditions such as thyroiditis and primary biliary cirrhosis also provides circumstantial evidence in support of the autoimmune PAH pathogenic theory, although more evidence is required to be confident.

Do PAH Treatments Work? - The three major classes of PAH-specific therapies include prostacyclin-analogues (such as iv epoprostenol, inhaled Iloprost, selexipag (IP prostacyclin-receptor-agonist)), endothelin-receptor blockers (also called endothelin-receptor antagonists,

or “ERAs”: including Bosentan and Ambrisentan), and phosphodiesterase-5 (PDE5)-inhibitors (such as sildenafil). Recent pooled studies of the use of these therapies in PAH revealed that they reduced death rates by around 40% with good side-effect profiles. The choice of treatment involves considerations including dosage-convenience (once or twice daily dosing preferable), potential drug interactions (e.g. sildenafil and nitrates), and risks of side-effects (e.g. liver function changes with ERAs). Traditional supportive therapies, including warfarin and diuretics are often appropriate, and selected circumstances may warrant treatment with calcium blockers, digoxin and oxygen. On average, PAH-specific treatments increase the 6MWD by 40m. Recent additions to the therapeutic toolbox include SGCs (stimulators of guanylate cyclase, such as riociguat) and now even cell-signalling modulators.

What Non-Drug Approaches May Be Useful? - Pooled studies of specialised exercise programs in PAH reveal improvements of at least 90m in 6MWD. These results represent over twice the benefit seen with drug therapies, and suggest that supervised exercise programs should be a universal part of PAH management.

Evidence suggests that management within a specialised multidisciplinary PAH clinic (incorporating expertise of nursing, allied health, cardiology, respiratory, rheumatology and immunology specialists) also improves patient outcomes and satisfaction

The impact of stress reduction and positive attitudes in chronic medical conditions is also well-recognised, with encouragement, reassurance, regular communication & assessment, and provision of accurate balanced up-to-date knowledge (avoiding pessimistic messages) being critical.

Are Support Groups Helpful? - Support groups provide access to many of the helpful factors mentioned above, and are increasingly becoming available. Current clinical, support, educational and research activities undertaken by Hunter Health in the field of PAH are supported by Autoimmune Resource & Research Centre (ARRC) in recognition of this close connection between autoimmunity and PAH. ARRC is a non-profit charitable organisation supported by medical trust funds, public donations and corporate endowments with the vision of providing world-best practice care, support, information, and research opportunities to individuals with systemic and organ-specific autoimmune conditions.

Pulmonary Hypertension Australia and Scleroderma Australia also provide valuable advocacy, educational and support roles.

What Can I Expect If I Have PAH? - Searches of the internet and even medical literature can paint an unduly pessimistic picture. Articles quote “3 year survival rates” which suggest to the layperson that their days are numbered. The following points should be remembered:

- Much published data relies on older studies where less treatment options existed and sicker patients were recruited

- In the era of screening spurred by raised awareness, milder and earlier forms of PAH are being detected, which display better outcomes than those previously reported

- Even if we pool these studies and look at outcomes, we see that mortality falls by around 40% when current PAH agents are used

- Certain factors can move outcomes into still more favourable territory. These include a longer 6MWD, milder heart pressure and function changes, and more gradual symptom onset & progression

- Attitude influences outcomes

- “Incurable” does not mean unmanageable: remember that elevated cholesterol is incurable but manageable and “incurable” is not the same as “terminal”

- Great research efforts are currently being poured into the field, broadening treatment options rapidly

What Does The Future Hold? - While PAH therapies are advancing rapidly in their effectiveness and safety, there is still vigorous debate about the following issues:

* How much to treat numbers: is PAH like SHT, where we should aim for certain measured readings? There is a growing belief that treatment based upon symptoms alone is inadequate, but the general verdict is still out

* Is PAH best defined using static (resting) or dynamic (exercise-related) tests: most authorities agree that exercise function and capacity are important, and revisions of current guidelines recommending against functional studies such as stress echo (echo after exercise) may well be revised.

* How early to treat: is earlier treatment better in terms of improving patient health (both how they feel and their ultimate lifespan)?

Arguably, PAH may well go the way of systemic HT. Screening for PAH will occur (not with a “cuff”, but with an “echo”); unacceptable levels of pressure & resistance elevation will be defined; treatments will be introduced early to avert complications; and quality & duration of life will improve. Perhaps it will soon be unthinkable to defer PAH therapy until breathlessness occurs. Until then, we gather information and treat where circumstances are compelling. Sensitive screening tests like the “cuff” and the “echo” have moved systemic hypertension and PAH from dire medical emergencies to milder manageable chronic conditions. History does repeat, but lessons learned from history tell us that most medical conditions, through earlier detection and intervention, have become less dire and more compatible with good outcomes.

Best wishes

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