New-onset dyspnoea in the young adult: consider the serious causes

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It is prudent to consider potentially serious causes in a young adult patient presenting with insidious-onset dyspnoea. Such causes include heart failure due to cardiomyopathy and pulmonary arterial hypertension.

Dyspnoea is a common presenting symptom in general practice. It is a complex process that involves respiratory motor activity and feedback from sensory receptors in the airways, lungs and chest wall. It may be the only complaint in a patient presenting with cardiorespiratory disease, or be associated with a variety of other symptoms. Dyspnoea in a young adult (age 18 to 35 years) encompasses a wide variety of diagnoses, but consideration of serious pathologies is important, particularly in a patient who rarely presents for health care.

This article focuses on the young adult presenting with insidious-onset dyspnoea as the only symptom.

CAUSES OF DYSPNOEA IN THE YOUNG
Dyspnoea has a multitude of causes, ranging from benign to life threatening (see the box on page 40). These can be considered in terms of organ systems, including the airways, lungs, heart, blood and neuromuscular system. In prospective studies, cardiac or respiratory disease is the primary aetiology in three-quarters of cases. Asthma is by far the most common diagnosis, with 12% of Australians suffering from the disease. Acute pneumonia, pneumothorax, pulmonary embolism, anaemia and anaphylaxis are other common causes of dyspnoea among young patients.

Importantly, uncommon but potentially life-threatening diseases can present with dyspnoea.
as an isolated, insidious symptom in a young person who has been previously well. Dyspnoea is not a diagnosis; when there is no explanation for this symptom following appropriate investigation, the patient must be referred for cardiorespiratory specialist evaluation.

Two main pathologies significant in this regard are heart failure due to cardiomyopathy and pulmonary hypertension. Both these diseases can affect young people, are often insidious in onset and can be treated effectively. It is essential to consider these differentials, particularly in patients with new onset or undiagnosed symptoms where history, examination and simple investigations do not offer an immediate diagnosis.

HEART FAILURE DUE TO CARDIOMYOPATHY

Epidemiology and aetiology

The function of the heart may be affected in several ways: damage or loss of heart muscle, acute or chronic ischaemia, chronic hypertension, valvular disease and arrhythmia.

The genetic basis of dilated cardiomyopathy is increasingly being recognised. Of patients with dilated cardiomyopathy, 30% have a relative who has symptoms, signs or investigational findings consistent with the disease.6 However, inheritance is variable and genetic testing is not yet part of clinical practice.

Other causes of heart failure in the young patient include those listed below.

- **Myocarditis.** This may cause a variety of symptoms ranging from mild dyspnoea to pulmonary oedema, or even cardiogenic shock, and may result in long-term dilated cardiomyopathy.
- **Common viral infections.** These are the most common causes of heart failure, and include infection with enteroviruses, coxsackievirus B3 and adenovirus 7. HIV infection must also be considered.
- **Alcohol abuse.** Alcohol is a direct cardiotoxin, and patients consuming more than eight standard drinks a day for more than five years are at risk. Alcoholic cardiomyopathy is characterised by left ventricular (LV) dilation with reduced ejection fraction and without specific gross or histological findings.
- **Peripartum cardiomyopathy.** This is LV systolic dysfunction or signs and symptoms of heart failure presenting in the last month of pregnancy or the first five months postpartum.
- **Chemotherapy.**
- **Ischaemic cardiomyopathy.** Although this is a disease of an older population, occasionally young patients present with premature coronary disease. Given the
DYSNOEA IN THE YOUNG ADULT CONTINUED

COMMON CAUSES OF DYSNOEA IN THE YOUNG PATIENT

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>Myocardial ischaemia, Heart failure</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Asthma, Pneumonia, Pleural effusion, Pulmonary embolism, Pulmonary hypertension, Interstitial lung disease</td>
</tr>
<tr>
<td>Other</td>
<td>Acidosis, Anaphylaxis, Anaemia, Hyperventilation, Panic disorder, Upper airway obstruction</td>
</tr>
</tbody>
</table>

Other rare causes of heart failure include high output failure (anaemia), endocrine diseases, nutritional deficiencies, autoimmune diseases (such as systemic lupus erythematosus and sarcoidosis) and obstructive sleep apnoea.

Clinical assessment

A thorough history and examination are essential when considering a diagnosis of heart failure in a young patient. Breathlessness, tiredness and fatigue are characteristic. Cough without sputum is common, particularly at night. A change in exercise tolerance will help to assess both the severity and chronicity of the problem. It is useful to classify symptoms by the New York Heart Association (NYHA) functional class (Table 1). Paroxysmal nocturnal dyspnoea and orthopnoea have high specificity for heart failure. Ask patients about risk factors for ischaemic heart disease. Consider recent viral illness, alcohol intake and recent pregnancy as possible causes.

A young patient’s symptoms, particularly at initial presentation, correlate poorly with cardiac dysfunction and prognosis.

Clinical signs range from subtle to obvious in heart failure. Elevated pulse and low to low-normal blood pressure with cold peripheries are common. Signs of fluid overload include raised jugular venous pressure, distended neck veins, pitting oedema of the ankles, tender hepatomegaly and even ascites. Cardiac auscultation may reveal murmurs suggesting valvular dysfunction or a third heart sound (gallop rhythm). Respiratory findings include crackles and pleural effusion, which may be unilateral (more common on the right) or bilateral.

Investigation

Simple investigations can help to confirm or exclude a likely diagnosis of heart failure in patients before specialist referral. ECG, chest x-ray and basic laboratory tests (full blood count, measurement of electrolytes and serum glucose levels, and renal and liver function tests) should be performed in every patient. ECG findings are nonspecific but helpful if ischaemia or arrhythmias are found. Chest x-ray can detect pulmonary congestion and pleural fluid, as well as revealing other pulmonary causes of symptoms. Cardiomegaly (Figure) is a useful finding but may be absent, particularly in a young patient with an acute presentation.

Measurement of the natriuretic peptides brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are increasingly useful as part of the work-up of patients with suspected heart failure. A BNP of less than 100 pg/mL or NT-proBNP of less than 400 pg/mL makes a diagnosis of heart failure unlikely in untreated patients. Values greater than 400 and 2000 pg/mL for BNP and NT-proBNP, respectively, make heart failure the likely diagnosis.

In cases of suspected myocarditis, viral titres may be useful. Check also HIV serology. Consider investigation for autoimmune or infiltrative diseases if there is clinical suspicion.

All young patients with a suspected diagnosis of heart failure should be referred for expert opinion. Echocardiography is the gold-standard investigation. It is widely available, rapid, noninvasive and safe. It can provide detailed information on cardiac anatomy, wall motion and dilation, and valvular function. It requires skilled operation and interpretation, and there is a high level of inter-observer variation.

Other investigations helpful in the evaluation of patients with heart failure include exercise testing, pulmonary function testing, and right and left heart cardiac catheterisation. Cardiac MRI is increasingly used in competent centres. Endomyocardial biopsy may guide management in a selected group of patients, particularly if considered for transplantation.

### Table 1. New York Heart Association (NYHA) Functional Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Level of impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No limitation of physical activity</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of physical activity</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of physical activity</td>
</tr>
<tr>
<td>IV</td>
<td>Unable to carry out any physical activity without discomfort</td>
</tr>
<tr>
<td></td>
<td>Symptoms of cardiac insufficiency at rest</td>
</tr>
</tbody>
</table>

NYHA functional class (Table 1). Particularly at initial presentation, correlate poorly with cardiac dysfunction and prognosis.
Management

Once a diagnosis of heart failure has been made, management has three main objectives:

- treating symptoms
- preventing further myocardial damage
- improving prognosis.

Patients with severe symptoms often need hospitalisation and aggressive diuresis. Modifiable factors, if present, need to be addressed. For example, patients with coronary artery disease require immediate investigation and treatment; patients with alcoholic cardiomyopathy must abstain from alcohol and may require intense support to do so.

As with many chronic diseases, patient education and nonpharmacological management is paramount in heart failure. A range of self-care management topics must be discussed, including symptom recognition, weight monitoring, and sodium and fluid restriction and adherence.

Young patients are often psychologically distressed at the time of diagnosis and require quite intensive counselling and reassurance. A list of essential topics, including nonpharmacological management strategies, to discuss with patients is shown in the box on this page.

A range of pharmacological agents are used in heart failure, and it is important to consider the impact of each drug on symptoms and prognosis, as well as the potential for complications and side effects. The mainstays of drug therapy are ACE inhibitors and beta blockers. They should be commenced once the patient has been stabilised with diuretics and uptitrated to the maximum tolerated doses. The flowchart on page 43 summarises the steps in the treatment of young patients with heart failure. Most clinical trials on heart failure have been conducted in elderly populations with systolic dysfunction and a low ejection fraction, and care must be taken applying the results of these trials to young patients.

Multidisciplinary heart failure clinics and home-based interventions have been shown to be beneficial in patients with chronic heart failure. Australian studies have shown such interventions significantly reduce unplanned readmission and death, as well as being cost effective. These programs can assist the primary care physician and cardiologist by adding specialty nursing care and reinforcing education. Exercise training is indicated for all stable patients with heart failure, and may be performed as part of an outpatient program or at home.

Pregnancy-induced (or peripartum) cardiomyopathy can be considered as a different entity from other cardiomyopathies, although the cause and mechanism remain unknown. Risk factors include older age, African origin, toxemia and hypertension. Treatment is similar to that for other forms of heart failure, but ACE inhibitors must be avoided during pregnancy due to potential toxic effects on the fetus. There is a higher rate of spontaneous recovery than for other forms of dilated cardiomyopathy, but morbidity and mortality remain high.

Prognosis

The diagnosis of cardiomyopathy is unquestionably life changing in a young patient and, despite advances in therapy, prognosis remains guarded. The clinical course is highly variable, but patients with severe symptoms at diagnosis have a poorer prognosis. Overall, the five-year survival is approximately 50%, with most deaths due to progressive heart failure and complications. Adult patients with myocarditis who have symptoms have a four-year mortality of 56%, Symptoms and prognosis in patients with alcoholic cardiomyopathy may improve with abstinence, but alcoholics have a worse prognosis overall.

Sudden cardiac death due to arrhythmia is a common cause of death in patients with dilated cardiomyopathy. There is now good evidence that insertion of an automatic implantable cardioverter defibrillator is beneficial in patients with a LV ejection fraction of less than 35% and NYHA functional class II or III, with or without previous ventricular arrhythmia. Patients resistant to medical
therapy may be referred for consideration of cardiac transplantation if there are no contraindications. In carefully selected patients, five-year survival may be as high as 65 to 75% following transplantation.16

PULMONARY ARTERIAL HYPERTENSION

Pulmonary arterial hypertension (PAH) is a rare disease, and often a difficult diagnosis to make. However, the recent discovery of therapies that can improve symptoms and survival has led to a great deal of interest in the area and recognition that early diagnosis is essential.

PAH is characterised by increased pulmonary vascular resistance and pulmonary arterial pressure that can lead to right heart failure and death. Although findings on a transthoracic echocardiogram may suggest PAH, a right heart study is essential to confirm the diagnosis, which is characterised by:

- a mean pulmonary arterial pressure of more than 25 mmHg
- an increased pulmonary vascular resistance of greater than 3 Wood units
- a normal pulmonary capillary wedge pressure of less than 15 mmHg.

Epidemiology and aetiology

A recently published, large registry of patients with PAH found that the mean age at diagnosis was 50.1 years, and that 80% of patients were female.17 Importantly, most patients (74%) had moderate to severe symptoms at the time of definitive diagnosis, with NYHA class III or IV dyspnoea. The mean time between symptom onset and diagnosis was 2.8 years.

The cause of PAH is idiopathic in about 50% of patients. In the other half it is associated with other diseases, including collagen vascular disease/connective tissue disease (25%), congenital heart disease (10%), portal hypertension (5%), drugs/toxins (5%) and HIV infection (2%). Other diseases such as COPD and thromboembolic disease may cause PAH, but these are less likely in a young patient.

Clinical assessment

Young patients with PAH usually present with dyspnoea and a paucity of other symptoms. The onset is insidious, with gradually reduced exercise tolerance over months to years, often with significant breathlessness during daily activities at presentation. Associated symptoms may include fatigue, chest pain, presyncope or palpitations.14 Patients have often been trialled on inhalers for asthma without success.

Physical examination is often surprisingly normal, and out of keeping with the patient’s symptoms. The most important clue is a loud P2 (pulmonary component of the second heart sound), heard best at the left upper sternal border. This occurs in nearly all patients. On careful auscultation, many also have right-sided
S3 or S4 heart sounds or tricuspid regurgitation. Patients may even present with right heart failure. The presence of wheeze, crackles, pulmonary oedema or muscle fatigability suggests an alternative diagnosis.

**Investigation**

Initial investigations for PAH should include an ECG, chest x-ray and pulmonary function tests. The ECG may be normal or show sequelae of PAH, including right ventricular (RV) hypertrophy, right atrial enlargement or right bundle branch block. Similarly, the chest x-ray may appear normal, but often shows prominent proximal pulmonary arteries and peripheral oligoemia. RV hypertrophy or right atrial enlargement may also be visible. Pulmonary function tests will exclude airway obstruction (normal FEV1 and FVC), with normal lung volumes but decreased diffusing capacity. Basic laboratory tests, including full blood count, urea and electrolyte measurements, and thyroid and liver function tests, should also be requested, but are likely to be normal.

The gold-standard test for diagnosing PAH is right heart catheterisation; however, this is an invasive and expensive procedure, carried out only in specialised centres. Transthoracic echocardiogram is the initial investigation of choice. Estimation of RV systolic pressure can be performed by measurement of the tricuspid regurgitant jet. This is an imperfect assessment, which may underestimate or overestimate the true value, and in some patients with significant pulmonary hypertension there is no measurable regurgitation.

A Perth study found that the RV systolic pressure could not be estimated in 13% of patients, and only about half of patients with PAH suspected on echocardiogram had the diagnosis confirmed in the right heart study. Other signs of PAH on echocardiogram include RV hypertrophy, enlarged right atrium and prolonged RV ejection time. LV size and function should be normal, and a shunt (bubble) study should be performed to exclude congenital heart disease.

Further assessment of patients with suspected PAH should be performed with specialist consultation. Right heart catheterisation is the last step in the process; it is invasive and has risks. It is carefully considered after review at a specialised PAH clinic. Rural patients would need to travel to a major centre for review before being considered for right heart catheterisation. Pulmonary hypertension clinics now exist at many teaching hospitals, with multidisciplinary input. Respiratory physicians and cardiologists often work closely in assessment and management of patients. Secondary causes of PAH must be considered: connective tissue disease, interstitial lung disease, chronic thromboembolic disease, collagen vascular disease and a number of other pathologies must be excluded.

Right heart catheterisation is essential to the diagnosis and treatment of patients with PAH, and allows real-time assessment of response to vasodilator therapy. A small proportion of patients responds to calcium channel antagonists, and may be successfully treated with these cheaper and easy to use agents.

Once PAH is confirmed, a six-minute walk test is the test of choice for evaluating functional capacity, response to treatment and prognosis.

**Management**

There is no known cure for idiopathic PAH; however, several pathophysiological pathways can be targeted and this has led to the development of a number of successful therapies, although the overall benefit of these therapies is modest. These processes are listed in Table 2, although it is not yet clear whether these processes cause PAH or are manifestations of the disease. Drugs available for use in patients with PAH are listed in Table 3.

Combination therapy with drugs from different classes may be beneficial in

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**TABLE 2. PATHOPHYSIOLOGICAL PATHWAYS IN PAH**

<table>
<thead>
<tr>
<th>Molecule/protein</th>
<th>Physiological action</th>
<th>Change in PAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostacyclin</td>
<td>Potent vasodilator</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>Antiproliferative</td>
<td></td>
</tr>
<tr>
<td>Endothelin 1</td>
<td>Potent vasoconstrictor</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td>Pulmonary artery smooth muscle proliferation</td>
<td></td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Vasodilator</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>Inhibits smooth muscle production</td>
<td></td>
</tr>
</tbody>
</table>

**ABBREVIATION:** PAH = pulmonary arterial hypertension.
patients with symptoms not well controlled with a single drug. However, this approach is not yet approved in Australia and patients must be part of a trial to access such therapy. Given the poor prognosis and overall modest benefit with current drug therapies, the search is on for novel agents to treat the disease. Current therapies under trial include soluble guanylate cyclase stimulators/activators, tyrosine kinase inhibitors and serotonin antagonists.

Patients with PAH associated with connective tissue disease, drugs and toxins or HIV infection are also candidates for the treatments listed above, because the pathophysiology is thought to be similar. However, patients with PAH secondary to left heart failure or chronic lung disease are best managed with treatment of the underlying disease.

Nonpharmacological options for PAH are limited. Physical activity, as part of a co-ordinated rehabilitation program, may provide some benefit, but patients must be closely monitored to avoid severe dyspnoea or syncope.21

Despite aggressive treatment, many patients continue to deteriorate. Young patients without contraindications may be considered for lung or heart-and-lung transplantation. Prognosis without treatment is very poor, with median survival approximately 2.8 years from diagnosis for patients with idiopathic PAH. A recent meta-analysis of patients receiving active therapy showed 43% decreased mortality over a short time period (average three months).22 Follow up in one recent endothelin receptor antagonist trial estimated the two-year survival to be 88%.

**SUMMARY**

Young patients presenting with dyspnoea are common in general practice. Although most will have a readily identifiable cause, others present more of a challenge.

In a young adult patient presenting with insidious-onset dyspnoea, it is prudent to consider potentially serious causes. Heart failure due to cardiomyopathy may be idiopathic, familial or secondary to other disease, and there are often clues in the history, examination and basic investigations. PAH may present with isolated dyspnoea and few clinical signs, or with right heart failure. For both diseases, echocardiogram is the single most useful screening test, and should be ordered promptly if ECG, chest x-ray and blood tests fail to identify a cause. Referral for specialist opinion must be considered. An early diagnosis of cardiomyopathy or PAH in a young person may result in treatment that relieves symptoms, improves exercise tolerance and reduces mortality. **MT**

**REFERENCES**

A list of references is available on request to the editorial office.

**COMPETING INTERESTS:** None.

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**TABLE 3. DRUGS USED IN PAH**

<table>
<thead>
<tr>
<th>Target</th>
<th>Class</th>
<th>Drug</th>
<th>Route</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostacyclin</td>
<td>Prostanoids</td>
<td>Epoprostenol</td>
<td>Continuous IV infusion</td>
<td>Used in major centres only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treprostin</td>
<td>Continuous IV/SC infusion</td>
<td>Used in major centres only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iloprost</td>
<td>Inhaled</td>
<td></td>
</tr>
<tr>
<td>Endothelin receptor antagonists</td>
<td>PDE5 inhibitors</td>
<td>Bosentan</td>
<td>Oral</td>
<td>First line, monitor LFTs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ambrisentan</td>
<td>Oral</td>
<td>Causes peripheral oedema</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>PDE5 inhibitors</td>
<td>Sildenafil</td>
<td>Oral Marketed as Revatio for PAH</td>
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<tr>
<td>Peripheral vasodilation</td>
<td>Calcium channel blockers</td>
<td>Nifedipine</td>
<td>Oral Only about 10% of patients respond</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diltiazem</td>
<td>Oral Only about 10% of patients respond</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amiodipine</td>
<td>Oral Only about 10% of patients respond</td>
<td></td>
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</table>

**TABLE 3. DRUGS USED IN PAH**

**ABBREVIATIONS:** IV = intravenous; LFTs = liver function tests; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; SC = subcutaneous.
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