COPD and CVD

The heart of the matter

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Chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) are frequently associated, with worse outcomes when the two coexist. Hence, it is crucial that patients with coexisting COPD and CVD are managed effectively.

Key points

- **Globally, cardiovascular disease (CVD) is the leading cause of death and chronic obstructive pulmonary disease (COPD) is ranked third.**
- **COPD is also the third leading cause of total disease burden in Australia.**
- **COPD and CVD are frequently associated, resulting in worse outcomes than for either disease on its own.**
- **The diagnosis of CVD in patients with COPD can be elusive due to overlapping symptoms, interacting pathologies and challenges to diagnostic testing as a result of hyperinflation and dyspnoea.**
- **Medications for CVD improve survival but patients with COPD miss out on crucial cardiac therapies due to concerns about exacerbating COPD symptoms, even though the existing evidence suggests that such concerns may be unwarranted.**
- **CV death remains a major cause of mortality in patients with COPD; therefore, CVD should be aggressively treated, particularly as our treatments for COPD remain largely symptomatic.**

Chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) are common conditions that are frequently associated. Risk factors and symptoms overlap, making diagnosis of cardiac disease (CD) more difficult. Medications for CVD improve survival but patients with COPD miss out on crucial cardiac therapies due to concerns about exacerbating COPD symptoms, even though the existing evidence suggests that such concerns may be unwarranted.

COPD is a common condition, with 9% of Australian men and 12% of Australian women aged 40 years and above having spirometrically defined COPD, with the ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) falling below 0.7 and FEV_1 less than 80% of predicted normal.[1] This corresponds to disease sufficiently severe to cause symptoms and impact daily activities.[1] Globally, CVD is the leading cause of death and COPD is ranked third.[2] COPD is also the third leading cause of total disease burden in Australia, indicating that it is a major contributor to morbidity in the years preceding death.[3]

COPD is associated with many comorbidities (Figure 1).[4] In particular, CVD and COPD are frequently associated, with worse outcomes when the two are combined. Patients with COPD are much more likely to be diagnosed with coronary artery disease (CAD), dysrhythmia, heart failure (HF), pulmonary circulatory disorders and arterial diseases than patients without COPD.[5] These diseases share common risk factors such as ageing, smoking and sedentary

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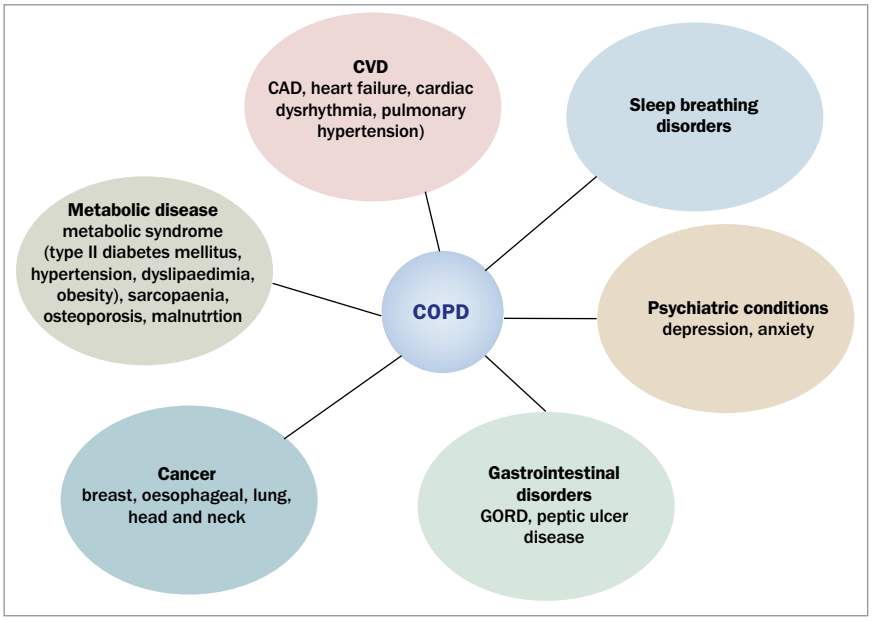

Figure 1. Comorbidities commonly associated with COPD.

Abbreviations: CAD = coronary artery disese; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; GORD = gastro-oesophageal reflux disease.

lifestyle. Even so, the impaired lung function seen in COPD is an independent risk for CVD mortality.[6-8] COPD patients with comorbid CVD have worse lung function, worse quality of life and more frequent exacerbations.[4,9-11] Indeed, in patients with moderately severe COPD, mortality because of CVD is higher than mortality as a result of respiratory failure.[6-8]

Due to the high burden of disease from these two conditions, it is crucial that patients with coexisting COPD and CVD are managed effectively. The aims of this article are to raise awareness of the high prevalence of CVD in COPD and its adverse impact on patient outcomes, and to discuss important management issues. We will focus on HF, ischaemic heart disease and dysrhythmia, the most relevant cardiac conditions.

Pathophysiology of CVD and COPD

The interaction between COPD and CVD is complex (Figure 2). Patients with COPD have greater arterial stiffness and plaque content vulnerable to rupture, which increases risk for ischaemic cardiac events.[12] Significant lung hyperinflation may directly compress the ventricles, resulting in impaired ventricular function.[13,14] Compared with people who do not have COPD, those with COPD exhibit higher rates of both systolic and diastolic dysfunction, and either ventricle may be affected.[15] Excess sympathetic activity seen in COPD has been implicated in both COPD-associated HF and dysrhythmia. Loss of pulmonary vascular surface area, hypoxaemia and resultant chronic vasoconstriction lead to pulmonary hypertension, elevated right ventricular filling pressures and ultimately right heart failure.

Recognising CVD in patients with COPD

The diagnosis of CVD in patients with COPD can be elusive due to overlapping symptoms, interacting pathologies and challenges to diagnostic testing as a result of hyperinflation and dyspnoea. Indeed, severe COPD exacerbations invariably impact both cardiac and respiratory systems and, on occasion, can be acute cardiac events masquerading as lung disease. It is therefore important that clinicians actively seek out underlying CD and CVD risk factors, as timely intervention may have an impact on survival. For patients with stable COPD there is obviously no substitute for a careful, detailed clinical history and a focused physical examination looking for features suggesting coexisting CD. Investigations that might aid in the diagnosis of CD include a 12-lead ECG, chest x-ray, natriuretic peptide testing (brain-type natriuretic peptide [BNP] or N-terminal prohormone [NT-proBNP]), transthoracic echocardiography and tests for myocardial perfusion.[16] CVD risk factors such as hypertension, dyslipidaemia and impaired glycaemic control should be actively sought and addressed as per guideline recommendations.

If there are symptoms to suggest an acute coronary syndrome, such as new chest pain or breathlessness that is worse than usual, then performing a repeat ECG and measurement of biochemical markers of myocardial injury such as troponin T or troponin I may confirm the need for an urgent referral to the nearest hospital emergency department, where invasive or noninvasive assessments of coronary ischaemia should be considered. If in doubt, this is the best course of action.

Case scenario 1

Ross, aged 65 years, a 70 pack-year smoker with severe COPD, has a strong family history of CAD. He presents eight times within three years with severe COPD exacerbation and acute hypercapnic respiratory failure, requiring ventilatory support. His presentations are notable for the rapid onset of symptoms, elevated troponin T level and an absence of infective or inflammatory features. In 2017, he presented with a rapid broad complex tachycardia and was found to have cardiomyopathy, which was appropriately treated with an ACE inhibitor and beta blocker. Interpretation of his echocardiogram was difficult because of severe hyperinflation. Despite a normal coronary angiogram and starting medical therapy, Ross had a catastrophic presentation in 2019 with ST-elevation myocardial infarction (MI), and was left with severe ischaemic cardiomyopathy. His functional capacity remains extremely limited due to breathlessness.

This case illustrates significant coexisting CD in a patient with COPD and CV risk factors, highlighting the complex interactions between cardiac and respiratory pathophysiology during COPD exacerbations

and the difficulty in making the diagnosis. His presentation provides clues to cardiac involvement; namely, the rapidity of symptom onset, ongoing frequent exacerbations despite guideline-directed COPD treatment and an exacerbation pattern characteristically lacking infective or inflammatory features.

Pharmacological management

Given the complex interactions between pulmonary disease and CVD, it is important that both conditions are managed optimally. Concerns about CVD treatments worsening symptoms in COPD result in these patients missing out on medications that benefit survival. Likewise, bronchodilator treatments used for COPD can potentially increase the risk of CV events. Each condition should be managed on its own merits, using guideline-directed therapies. The treating doctor may be placed in the position of prescribing medications with opposing actions, such as beta agonists and beta blockers, which might seem counterintuitive but is actually quite safe.[17,18] To this end, when setting treatment goals with patients, it is important to remember that cardiac treatments such as ACE inhibitors and beta blockers improve survival in patients with CD, whereas COPD treatments help symptoms and decrease exacerbations, all of which are important goals.

As there are many medications used to treat COPD and CD, this article will limit discussion to the most relevant ones, including those that are locally available in Australia, those underused according to local and international guidelines and those with potential or actual adverse effects. It is challenging to weigh up the evidence for adverse medication effects, as the evidence is mainly retrospective; randomised trials were mostly designed to interrogate different outcomes; and participants in clinical trials are clearly quite different from the patients who attend our clinics.

COPD treatments

Although all bronchodilators are pro-arrhythmic at high dose and hence may increase cardiac work and risk of acute coronary events, there is no evidence that bronchodilator treatment used as per COPD-X guidelines should be modified for the presence of stable atrial fibrillation or other CVD.[19,20]

Short-acting beta-2 agonists (SABAs) may increase the risk of CV events through stimulation of sympathetic activity and effects on potassium concentrations.[21] Similarly, short-acting muscarinic antagonists (SAMAs) suppress parasympathetic control of heart rate, which could also lead to tachyarrhythmia and/or coronary ischaemia.[22] On the other hand, short-acting bronchodilators may have a positive impact on CV risk by improving dyspnoea, oxygen delivery and pulmonary haemodynamics in the setting of COPD exacerbation.

Well-conducted trials and meta-analyses have demonstrated that long-acting beta-2 agonists (LABAs), long-acting muscarinic antagonists (LAMAs) and combination LABA/LAMAs are likely safe to use for COPD in patients with CVD.[23-25] One potential area of concern, however, is the expanding range of new combination inhalers that may lead to patients inadvertently taking two LABAs or two LAMAs. Combining two long-acting bronchodilators of the same class increases the risk of adverse effects for no additional symptomatic benefit.

Theophylline has a modest bronchodilator effect but its use is limited due to its narrow therapeutic index. Studies have shown an increased risk of arrhythmias, atrial fibrillation, supraventricular tachycardias and increased rates of CV death with theophylline use.[26,27] Theophylline is not currently recommended in Australia.[20]

Case scenario 2

Beverley, a 69-year-old woman with severe COPD presents with palpitations and shortness of breath. On examination, her heart rate is 120 beats/minute, blood pressure is 170/90 mmHg and oxygen saturation is 96%. Chest auscultation reveals reduced breath sounds and expiratory wheeze. ECG demonstrates sinus tachycardia. On further questioning, it transpires that Beverley recently ceased her fluticasone/salmeterol inhaler. Her physician had replaced it with tiotropium/olodaterol and fluticasone inhalers. Instead of taking tiotropium/olodaterol once daily, she was taking it twice daily, which resulted in her taking double the recommended dose.

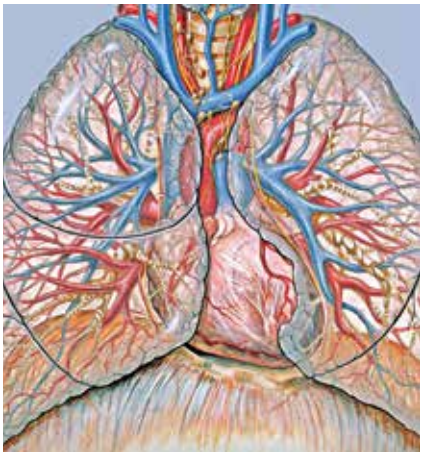

Figure 2. The interraction between chronic obstructive pulmonary disease and cardiovascular disease is complex.
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Beverley was taking an inappropriately high dose of tiotropium/olodaterol, which likely led to the palpitations. Before starting tiotropium/olodaterol, Beverley had been on fluticasone/salmeterol 250/25 mcg (two inhalations, twice a day, via metered dose inhaler and volumatic spacer) for several years. This case highlights the potential for inhaled medication errors in patients with COPD and the complications that may ensue. It also highlights the important role that GPs can play to ensure the appropriate dose and regimen for inhaled medications (Figure 3).

Pulmonary rehabilitation

Pulmonary rehabilitation (PR) plays an integral role in the management of patients with COPD. It improves shortness of breath, exercise capacity and health-related quality of life.[28] Similarly, cardiac rehabilitation is a key component of secondary prevention in patients with established CD.[29,30]

Although the effect of PR on CV risk is not well established, there are overlapping features between pulmonary and cardiac rehabilitation programs, such as exercise and nutrition, that are likely to have a positive impact. Supervised exercise therapy is generally safe in patients with CVD, with rates of major CV events ranging from 1/50,000 to 1/120,000 patient-hours of exercise.[31]

Green tick indicates therapies that can be used together			SABA	SAMA	LAMA	LABA	LABA/ LAMA	ICS/ LABA	ICS/ LAMA/ LABA
SABA	• salbutamol (Ventolin™, Airomir™, Asmol™)	• terbutaline (Bricanyl™)		✓	✓	✓	✓	✓	✓
SAMA	• ipratropium (Atrovent™)		✓			✓		✓	
LAMA	• tiotropium (Spiriva™) • glycopyrronium (Seebri™)	• aclidinium (Bretaris™) • umeclidinium (Incruse™)	✓			✓		✓	
LABA	• salmeterol (Serevent™) • formoterol (Oxis™, Foradile™)	• indacaterol (Onbrez™)	✓	✓	✓				
LABA/ LAMA	• indacaterol/glycopyrronium (Ultibro™) • umeclidinium/vilanterol (Anoro™)	• tiotropium/olodaterol (Spiolto™) • aclidinium/formoterol (Brimica™)	✓						
ICS/LABA	• fluticasone propionate/salmeterol (Seretide™) • fluticasone propionate/salmeterol (SalplusF™/ Cipla™) • budesonide/formoterol (Symbicort™)	• budesonide/formoterol (DuoResp™) • fluticasone furoate/vilanterol (Breo™)	✓	✓	✓				
ICS/LAMA/ LABA	• fluticasone furoate/umeclidinium/ vilanterol (Trelegy™)		✓						

Figure 3. Guide for ensuring that patients are not taking two medications of the same class. Excerpted from 'Stepwise management of stable chronic obstructive pulmonary disease (COPD)'.

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Treatments for heart failure

HF medications including beta blockers and ACE inhibitors have been shown to improve survival and reduce hospitalisation rates in patients with HF with a reduced ejection fraction (HFrEF).[32-35] Beta blockers also confer survival benefit for patients after acute MI. Nonetheless, patients with COPD are less likely to receive beta blockers in either setting and are less likely to undergo coronary revascularisation procedures, factors that may contribute to worse clinical outcomes.[36,37] Given the survival benefits, it is important that CAD and HF be treated as per national and international guidelines, regardless of the presence or severity of COPD.

Beta blockers

The benefits of beta blockers in patients with HFrEF are well established. Concerns surrounding the use of beta blockers in patients with COPD arise from their potential to induce bronchospasm. However, a reluctance to use beta blockers in patients with COPD may lead to suboptimal management of comorbid HFrEF or CAD, which arguably play a bigger role in long-term mortality. A Cochrane review found that short- and long-term use of cardioselective beta blockers in patients with COPD had no effect on FEV_1 or respiratory symptoms and did not adversely impact the patients' response to beta-2 agonist treatment.[18] These results were consistent regardless of whether patients had severe airways disease or COPD with reversible airflow obstruction.

ACE inhibitors and angiotensin receptor blockers

Use of ACE inhibitors and angiotensin receptor blockers (ARBs) in HF improves survival but cough is a common side effect associated with ACE inhibitors that may affect up to 20% of patients.[38] ARBs do not cause cough and therefore may be preferable in patients with COPD.

Management of comorbid COPD and CVD

Despite the safety of cardiac medications in patients with COPD, beta blockers and ACE inhibitors/ARBs are still underused.[39,40] The Global Obstructive Lung Disease (GOLD) strategy states that, in general, comorbidities should be treated according to usual standards regardless of the presence of COPD.[18] Hence, in patients with COPD, beta blockers are recommended after MI, while patients with HFrEF should start beta blockers and ACE inhibitors at the lowest dose with uptitration as tolerated.

GPs play a crucial role in identifying underlying CVD in patients with stable COPD and in recognising the cardiac contribution to symptoms, especially in COPD patients with poor response to COPD treatments. Optimising lifestyle parameters remains the cornerstone of preventive medicine and all patients should be encouraged to stop smoking, remain active and maintain a healthy weight. Blood pressure and lipid levels should also be treated to guideline-recommended targets. With the abundance of combination inhalers on the market, GPs should ensure that patients are not taking two medications of the same class (Figure 3). Finally, GPs play an integral role in co-ordinating care of patients who need specialist input for either their heart or lung disease to avoid the adverse impacts of fragmented care.

Conclusion

CVD is a common comorbidity in patients with all severities of COPD. The diagnosis of coexisting CD can be difficult given overlapping signs and symptoms, and therefore it needs to be actively considered in all patients. CV death remains a major cause of mortality in patients with COPD; therefore, CVD should be aggressively treated, particularly as current treatments for COPD are largely symptomatic. **RMT**

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A list of references is included in the online version of this article www.respiratorymedicinetoday.com.au.

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