Review Article

Coexistent Chronic Obstructive Pulmonary Disease-Heart Failure: Mechanisms, Diagnostic and Therapeutic Dilemmas

Sunil K. Chhabra and Mansi Gupta

Department of Cardiorespiratory Physiology, Viswanathan Chest Hospital, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India

ABSTRACT

Mortality in chronic obstructive pulmonary disease (COPD) is more often due to cardiac rather than respiratory causes. The coexistence of heart failure (HF) and COPD is frequent but remains under-diagnosed. Both conditions share several similarities including the age of the population affected, a common risk factor in smoking and symptoms of exertional dyspnoea. There is also a strong possibility of COPD promoting atherosclerotic vascular disease through systemic inflammation. Both the conditions are punctuated by episodes of acute exacerbations of symptoms from time to time where differentiation between these two can be especially challenging. Although coexistence of the two is common, more often, only one of the two is diagnosed resulting in under-treatment and unsatisfactory response. Awareness of co-occurrence is essential among both pulmonologists and cardiologists and a high index of suspicion should be maintained. The coexistence of the COPD and HF also poses several challenges in management. Active search for the second disease using clinical examination supplemented with specialised investigations including plasma natriuretic peptides, lung function testing and echocardiography should be carried out followed by appropriate management. Issues such as adverse effects of drugs on cardiac or pulmonary function need to be sorted out by studies in coexistent COPD-HF patients. Caution is advised with use of β_2-agonists in COPD when HF is also present, more so in acute exacerbations. On current evidence, the beneficial effects of selective β_1-blockers should not be denied in stable patients who have coexistent COPD-HF. The prognosis of coexistent COPD and HF is poorer than that in either disease alone. A favourable response in the patient with coexistent COPD and HF depends on proper evaluation of the severity of each of the two and appropriate management with judicious use of medication. **[Indian J Chest Dis Allied Sci 2010;52:225-238]**

Key words: Chronic obstructive pulmonary disease, Corornary artery disease, Atherosclerosis, Heart failure, Brain natriuretric peptide, Beta blockers, Review.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a very common disease largely affecting moderate-to-heavy smokers. It is one of the leading causes of morbidity and mortality in adults all over the world. Other causes of non-cancer mortality including coronary artery disease (CAD) and stroke have shown a consistent downward trend in the past two decades. However, COPD continues to increase.[1] It is a major cause for health-care utilisation, emergency department visits and hospitalisations.[2] The epidemiological scenario is expected to worsen and the World Health Organization predicts that COPD will become the third leading cause of death (currently fourth) and the fifth leading cause of disability (currently twelfth) worldwide by the year 2020.[3,4] It usually manifests in the middle-age with symptoms of dyspnoea on exertion and cough, usually with expectoration. With increasing severity of disease, patients experience acute exacerbations of COPD (AECOPD), characterised by increased severity of these symptoms requiring a change in the level of treatment. Patients with AECOPD often require hospitalisation, including intensive care admissions for accompanying respiratory failure.

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality all over the world. The major cardiovascular disease is atherosclerosis affecting the coronary, cerebral and peripheral circulation. Atherosclerosis in the coronary circulation is labelled as CAD and manifests itself by causing compromised blood flow insufficient to meet the demand leading to ischaemic injury and ultimately death (infarction) of the myocardial tissue. Usually, it is the myocardium of the

[Received: August 16, 2010; accepted: August 24, 2010]

Correspondence and reprint requests: Dr S.K. Chhabra, Professor and Head, Department of Cardiorespiratory Physiology, Viswanathan Chest Hospital, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi - 110 007, India; Phone: 91-011-27667102, 27667667, 27667441, 27666182; Fax: 91-011-27666549; E-mail: skchhabra@mailcity.com

left ventricle (LV) that bears the brunt of CAD as it has the bulk of the cardiac muscle, although the right ventricular (RV) blood supply may also be affected. Ischaemia and infarction result in reduced systolic contractility of the LV leading to reduced cardiac output, with a failure to adequately meet the demand for its increase, especially on exertion and during stressful situations, a condition referred to as heart failure (HF). The risk of CAD is increased by smoking, increasing age, obesity, dyslipidemia, diabetes mellitus, hypertension with contributions from genetic predisposition, male gender and life-style factors. The high prevalence of these risk factors and conditions in all populations underlies the high worldwide prevalence of CAD and its consequences including HF. While other conditions, such as valvular heart diseases and cardiomyopathies, can also impair cardiac function leading to HF, CAD (with or without hypertension) remains by far the commonest cause.

Despite advances in the control of CVDs, such as myocardial infarction (MI), HF is the only cardiovascular disease (CVD) whose incidence and prevalence continues to increase.[5] An accurate estimate of the disease burden due to HF is difficult to gather because of the vast number of patients with asymptomatic LV dysfunction. As the population ages, there is a shift towards a greater prevalence of clinical HF with preserved LV function. In fact, HF with normal ejection fraction (HFNEF) may account for up to two-thirds of patients older than 70 years.[6] Regardless of age, the life-time risk of developing HF is approximately 20% for all patients older than 40 years.[7]

Though the musculature of the two ventricles is anatomically connected and both beat in synchronisation activated by a common impulse, functionally the heart has traditionally been divided into right- and left-sided depending on the circulation it subserves — pulmonary and systemic, respectively. The two circulations are connected in series handling the same cardiac output, but work under widely different physiological conditions. The physiological role of the RV is largely to serve as a conduit leading to the low pressure pulmonary circulation. Therefore, it is provided with much less muscle compared to the left. Both right and left ventricles can fail. The term "congestive heart failure" (CHF) or simply HF, connotes a failing LV, unable to fulfill its mandated role of providing adequate cardiac output at rest and under conditions demanding an increase. Cor-pulmonale is the term used for an RV failure. Both HF and cor-pulmonale are functional failures, the important difference in causation being that while the former is usually a complication of a disease affecting the performance of the LV cardiac muscle, the ventricle in the latter responds to a disease affecting the lungs and/or the pulmonary circulation.

Like COPD, patients with HF associated with CAD also present in the middle-age with dyspnoea on exertion, and easy fatigability and sometimes cough. Similar to AECOPD, these patients too are prone to sudden worsening of function, called acute LV failure (LVF) or acute pulmonary oedema, especially with episodes of myocardial ischaemia/injury, and present with increased dyspnoea, orthopnoea and paroxysmal nocturnal dyspnoea. Being two very common diseases, COPD and CAD can be expected to occur concurrently in a large proportion of the ageing population. Further, the commonality of smoking in the causative factors of the two conditions would further increase the chances of co-occurrence. Thus, together, these become the leading cause of exertional dyspnoea in the middle-aged and older patients.

The link between COPD and CAD, however, goes beyond the above explanations. Any of the two may precede and the second may follow. The complication of COPD with CAD (and resultant HF) has been investigated far more extensively than the other way round and therefore, the present review largely focuses on the mechanisms and magnitude of the association, the resultant diagnostic challenges and therapeutic implications of HF (specifically left-sided) supervening on pre-existing COPD. In combined COPD-CAD, the similarity of presentations both in stable state and in acute exacerbations often causes diagnostic and therapeutic dilemmas.[8] Sorting out the contribution of each of these to the total symptomatology of the patient requires a thorough understanding of the pathophysiology of these conditions and specific investigations. Finally, it requires optimal management of both conditions to provide adequate relief to the patient.

Definitions

As defined by the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD),[9] *COPD* is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by air-flow limitation that is not fully reversible, usually progressive and associated with an abnormal inflammatory response of the lung to noxious gases and particles.

Heart failure (HF) has been defined by the European Society of Cardiology (ESC) as "clinical symptoms and objective evidence of cardiac dysfunction (systolic and/or diastolic).[10] Specifically, we shall refer to the term HF to connote a failing LV. The terms CHF and congestive cardiac failure (CCF) have been used to refer to the same pathophysiology in the literature.

Pulmonary hypertension (PH) is an elevation at rest in the mean pulmonary artery pressure (PAP) above 25mmHg with a pulmonary capillary wedge pressure (PCWP), left atrial pressure or LV end-diastolic pressure of less than 15mmHg and pulmonary vascular resistance (PVR) greater than three Wood units.

Cor-pulmonale is the consequence of PH caused by respiratory disorders and is defined as RV hypertrophy, dilatation or both.[11]

EPIDEMIOLOGICAL LINK BETWEEN COPD AND CAD

Epidemiological and observational studies have established that CVDs are common in COPD and a major cause of mortality too.[12] The need to establish the association between CVDs and COPD stems from the fact that more than 50% patients of COPD die of non-respiratory causes with respiratory failure, accounting for only 4% to 35% of COPD deaths. Mannino *et al*[13] analysed mortality trends among people who died with a diagnosis of obstructive lung disease from 1979 through 1993, using death certificate reports of 31 million decedents in the US. While 8.2% of these had a diagnosis of obstructive lung disease listed on their death certificates, less than half (43.3%) of these had obstructive lung disease listed as the underlying cause of death. In the Lung Health Study, cardiovascular deaths accounted for at least one-fourth (20%-25%) of the mortality cases throughout all stages in COPD patients.[14] The most common cause of mortality is cardiac failure.[15] Chronic obstructive pulmonary disease has now been well documented as an independent risk factor as well as predictor of CVD hospitalisation and mortality.[16] In fact, for every 10% decrease in forced expiratory volume in one second (FEV_1), all cause mortality increases by 14%, cardiovascular surgery (CVS) mortality increases by 28%, and non-fatal coronary events increase by 20 percent. Moreover, if the patient is having arrhythmias the risk of coronary events increases by two-folds.[17] Risk of hospitalisation and mortality due to cardiovascular causes is increased in patients with COPD by about 2.0- and 2.8-fold, respectively.[18]

CAD COMPLICATING COPD: POSSIBLE MECHANISMS

The association between COPD and CVDs arises from shared risk factors, most notably cigarette smoking, advancing age, systemic inflammation as well as contributing factors, such as use of cardio-stimulatory drugs like β-agonists and other medications, respiratory failure, hyperventilation leading to respiratory alkalosis, and the recently hypothesised concept of autonomic dysfunction.[19,20]

Ageing of the population increases the prevalence of all chronic diseases, which include CVDs (30% of projected total worldwide deaths in 2005), cancer (13%), diabetes (2%) and chronic respiratory diseases (7%), mainly COPD.[21] The number of patients with COPD and CAD (and HF) will rise with increasing life expectancy, as both conditions become increasingly more prevalent with age.

Smoking, the best established risk factor for COPD, is also a major risk factor for several other chronic diseases including CVDs, like atherosclerosis. Smoking plays a role via increased oxidative stress and systemic inflammation leading to inactivation of anti-proteinases, airspace epithelial damage, mucus hypersecretion, influx of neutrophils, and expression of proinflammatory markers.[22]

Systemic inflammation may provide the biological link between the two, *i.e.*, a common tumour necrosis factor-alpha (TNF-α) mediated pathogenesis underlying these diseases. Other common mediators may be substances, such as interleukin (IL)-6 and IL-18. Systemic inflammation is now believed to be contributory to the clinical manifestations and natural history of COPD, thus, becoming an essential component of the COPD disease process and also plays a key role in CAD and other manifestations of atherosclerosis.[23] Among the various inflammatory markers, the C-reactive protein (CRP) has been the focus of much of the research into the role of inflammation in atherosclerosis. The CRP is an acute-phase protein synthesised predominantly by the hepatocytes in response to tissue damage or inflammation. It reflects the total systemic burden of inflammation. Recent studies suggest that CRP is both a marker of inflammation and a factor in the pathogenesis of atherosclerosis, in part by activating endothelial cells and coronary artery smooth muscle cells. It has also been suggested that increased levels of CRP may play an important role in the progression of atherosclerosis in patients with COPD. Sin and Paul Man[23] reported that low-grade systemic inflammation was present in patients with moderate to severe airflow obstruction and was associated with increased risk of cardiac injury. The CRP levels have been reported to be higher in COPD patients than in controls and correlated with partial pressure of oxygen in arterial blood (PaO_2) and six-minute walk distance (6MWD) test.[24] Pinto-Plata *et al*[25] showed that this increase was not secondary to other factors, such as concomitant ischaemic heart disease (IHD) or smoking status, and observed that CRP levels were raised in COPD patients without clinically relevant IHD and independent of cigarette smoking, and reduced in patients with COPD using inhaled corticosteroids (ICS).[25] Another common link between atherosclerosis and COPD is the presence of oxidative stress in both the conditions. It has been suggested to

play an important role in the pathogenesis of both the conditions.[26,27]

Autonomic dysfunction (AD) is a known cause of mortality and a marker of poor prognosis in several disease states, such as diabetes mellitus, post-myocardial infarction and HF, and is increasingly being explored in COPD. Autonomic dysfunction predisposes the patient to risk of dysrhythmias and is also a potential link between COPD and CVD.

EFFECTS OF COPD ON CARDIAC FUNCTION

While its coexistence with HF is now well documented, as reviewed in the following sections, COPD also has direct effects on the cardiac function. Being a disease originating in, and largely affecting the lungs, its impact on the functioning of the RV is a direct complication frequently observed in the natural history of severe COPD. Heart failure, on the other hand, is a functional failure of the LV resulting from another disease, commonly CAD (often with hypertension), with which COPD is likely to have a cause-effect relationship as discussed above. A discussion of COPD associated with HF requires a review of its cardiac effects, both right- and left-sided. This is important as the RV enlargement may also affect the LV function. Several of the manifestations of RV failure resemble those of LV failure and both ventricles may fail together.

While the characteristic abnormality in COPD is an airflow limitation that is only partially reversible, and is usually progressive, the pulmonary involvement extends beyond the airways. A major contributor to airflow limitation is emphysema. Pulmonary vascular pathology is the other important lung involvement that contributes to the morbidity and mortality due to COPD. The consequence of the pulmonary vascular involvement is an increase in the PVR and PAP presenting an increased afterload to the RV. The increase in PVR is a consequence of a hypoxic vasoconstriction as well as permanent changes in the vascular structure and function (pulmonary vascular remodelling). Pulmonary vascular remodelling is believed to be a result of inflammatory changes induced by products of tobacco smoke but may also be induced or amplified by chronic hypoxaemia and may have a genetic basis to explain different susceptibilities towards developing PH among patients with COPD. A critical contributor to pathophysiology of PH is endothelial dysfunction producing an imbalance between vasoactive constrictor and dilator substances.[28] As COPD usually follows a progressive down-hill course, significant PH is a late-stage development occurring in patients with severe disease with chronic hypoxaemia. Pulmonary hypertension complicating COPD is classified under Group III of the fourth symposium (Dana Point) classification.[29]

The RV responds to increased PVR by gradually undergoing hypertrophy and later dilatation. Concentric RV hypertrophy is the earliest sign of RV pressure overload in patients with COPD. This structural adaptation of the heart does not alter RV and LV systolic function till later stages.[30] The effect on RV function cannot be predicted from PAP. The RV pre-load, after-load and contractility as well as its interaction with the LV, and the effects of intrathoracic pressure swings interact in a complex manner.[28] The increase in the end-diastolic volume (pre-load) of the RV due to dilatation maintains the cardiac output even as the RV ejection fraction decreases. The decreased elastic recoil and less negative intrathoracic pressures compress the two ventricles into one another opposing dilatation of the RV and tend to decrease the pre-load that eventually reduces the cardiac output. Lung volume reduction surgery (LVRS) improves the RV systolic function.[31] It has been shown that LV function is impaired in patients with severe emphysema due to small end-diastolic dimensions. The LVRS increases LV end-diastolic dimensions and filling, and improves LV function.[32] The effect on the RV increases with increasing severity of COPD. The FEV_1 and forced vital capacity (FVC) were negatively correlated with RV end-diastolic diameter and tricuspid annular plane systolic excursion and FVC positively correlated with systolic gradient across the tricuspid valve.[33]

As the two ventricles are in series, the reduced RV output reduces the LV pre-load. An increase in RV end-diastolic volume due to its dilatation also shifts the interventricular septum into the LV to reduce LV diastolic compliance and LV end-diastolic volume. On the other hand, the increased RV end-systolic pressure also serves to augment the LV emptying. Thus, a complex interplay of opposing forces determines the cardiac performance. Therefore, the LV ejection fraction is relatively preserved even in advanced emphysema.[34] Sudden increases in PAP as occur on exercise, or during sleep and acute exacerbations can overwhelm the capacity of the RV to adapt to the increased after-load and precipitate RV failure. Interestingly, there seems to be an adaptive tendency to concentric RV hypertrophy in COPD patients with left-sided HF. The RV mass divided by RV end-diastolic volume was higher in COPD patients with CHF than in those without concomitant CHF.[35]

Other mechanisms, such as hyperinflation, increased work of breathing, and raised intrathoracic pressures also have an impact on the LV functioning. Mechanisms of impaired LV filling in very severe COPD include alveolar hypoxia and related

pulmonary vascular changes, pulmonary hyperinflation, and ventricular interdependence. Alveolar hypoxia causes pulmonary-artery vasoconstriction and vascular remodelling, with increased pulmonary vascular resistance and impaired LV filling. Hyperinflation in very severe COPD can cause intrathoracic pressure to exceed venous pressure, with reductions in the blood volumes of both ventricles. A more likely mechanism in early, mild emphysema may be the subclinical loss of lung parenchyma and the pulmonary capillary bed.[36] These abnormalities of lung mechanics are compounded during exercise. At the time of exercise the sympathetic overdrive due to an increased demand by the tissues puts a pressure on the functioning of the heart that however falls short of the requirement, due to the exaggerated adverse lung mechanics during exercise.[37] Under such circumstances, a previously asymptomatic LV dysfunction may manifest clinically or an apparent dysfunction may exacerbate into overt HF, leading to increased filling pressures and reduced stroke volume in these patients. A symptomatic or advanced HF may in-turn activate the various compensatory mechanisms, like activation of renin-angiotensin-aldosterone system, sympathetic nervous system, vasopressin, as well as generation of pro-inflammatory cytokines to cause increased vascular resistance, increased heart rate, coronary insufficiency, altered renal blood flow, adverse remodelling, atrial fibrillations, etc, leading to ischaemia and arrhythmias further worsening the LV dysfunction and precipitating HF.[38]

Moreover, skeletal muscle alterations (decreased muscle mass and strength) in COPD, (due to deconditioning, disuse atrophy, systemic inflammation-induced protein catabolism, oxidative stress, and malnutrition) augment the LV strain and dysfunction under conditions of stress.[39] Other conditions and factors that may precipitate HF in COPD patients include acute infections, arrhythmias (MAT, AF), hypertensive emergencies, ischaemia, pulmonary embolism, severe anaemia, and use of cardiotoxic drugs.

MAGNITUDE OF THE ASSOCIATION

The coexistence of COPD and HF is well documented. The available data on concomitant prevalence of these conditions is quite alarming; however, the diagnosis of either of the two conditions is often delayed or overlooked depending on the dominating disease or the treating speciality.

HF in COPD

The risk ratio of developing HF is 4.5 in COPD patients compared to age-matched controls without COPD after adjustments for cardiovascular risk factors.[40] The rate adjusted hospital prevalence of HF is three times greater among patients discharged with a diagnosis of COPD compared with patients discharged without mention of COPD.[41] The Northern California Kaiser Permanente Medical Program has reported an age-adjusted relative rate of hospitalisation for HF of 5.55 (95% CI 4.71 to 5.73) and an odds ratio of HF as a co-morbidity of 8.48 (95% CI 7.65 to 9.40) in COPD patients compared with controls.[42] The reported prevalence of HF with systolic dysfunction among COPD patients varies (10%-46%), with the highest prevalence among those with AECOPD. The presence of unrecognised HF has been found as a significant cause of AECOPD. A prevalence of 21% of previously unknown HF was reported in patients with a history of COPD or asthma.[8,43]

The high prevalence of HF in patients with COPD indicates a direct effect of COPD on the LV function as discussed above. The association of COPD and HF has major implications for the management and alters the prognosis. The concomitant occurrence of the two conditions puts the patient in a state of double compromise due to the compounding effects of these two conditions on each other. The data on mortality reveals that the five-year mortality rates in patients with coexistent HF and COPD are as high as 69% as compared to 58% in patients with HF without COPD.[44] Moreover, the diagnostic and therapeutic challenges make the situation even worse for the handling clinician. The matter is further complicated by the commonly overlooked entities, *i.e.*, diastolic failure or the HFNEF (heart failure with normal ejection fraction). The LV diastolic dysfunction may be present in COPD patients with normal PAP and increases with RV after-load.[45]

COPD in HF

While the above studies clearly point to a substantial proportion of patients with COPD also suffering from HF, the reverse has not been investigated in much detail and only limited data is available. The CAD or HF do not cause COPD. Therefore, reports of COPD in HF reflect underdiagnosis of the former in patients with HF.

In a review of records of 34,587 patients with HF with a wide spectrum of severity, Havranek *et al*[46] reported that about one-third of patients had COPD. In a review of co-morbidities in HF, Dahlstrom[47] observed that COPD occurs in approximately 20% to 30% of HF patients. In another retrospective cohort study including 186 patients with LF systolic dysfunction and who had undergone a spirometry, the prevalence of COPD was 39.2% and severe COPD predicted worse prognosis.[48]

There is a gross underdiagnosis of COPD in patients with HF. Self-reported COPD only identifies a minority. The prevalence of COPD is high in both patients with systolic and non-systolic HF. In 532 patients admitted with HF, the prevalence of COPD was 35 percent. Only 43% of the patients with COPD were self-reported and one-third of these patients did not have confirmation on spirometry. The prevalence of COPD in patients with preserved LV ejection fraction was significantly higher than in patients with impaired LV ejection fraction.[33] In a total of 638 patients identified with a discharge diagnosis of HF, COPD was diagnosed in 106 (17%) patients. During follow-up, patients with COPD had a higher mortality.[49] In 391 patients admitted with HF, COPD was present in 25.1% of the patients.[50] Combined disease also presents a significant health-care burden in primary care. An analysis of cross-sectional data from 61 primary care practices (377 439 patients) in Scotland yielded a prevalence of COPD of 23.8% in patients with HF. It was similar in men and women.[51]

Chronic obstructive pulmonary disease, at least at severe degrees of airflow obstruction, predicts a worse prognosis in HF patients.[52] Analysis of data from the Norwegian Heart Failure Registry[53] of 4132 HF patients including 699 with COPD found the latter often on beta-blockers and with greater dyspnoea, although LV ejection fraction distribution was similar. The COPD independently predicted death.[53]

DIAGNOSTIC DIFFICULTIES

Unmasking HF in ambulatory patients with stable COPD requires suspicion and assessment of LV function to avoid delays in diagnosis and therapy of previously unrecognised HF. Recognising HF in the presence of COPD and *vice versa* is made difficult by similarities in symptoms and physical findings in the two conditions. Compounding the difficulties are the several similarities between cor-pulmomale and HF and the possibility of a biventricular failure. Hence, a high index of clinical suspicion is required along with a judicious use of specialised investigations. Coexistent COPD and HF often modifies classical findings in several of the investigations.

Symptoms and Signs

Exertional dyspnoea is the classical symptom of COPD and is also the clinical manifestation of HF due to LV dysfunction. Even cough can be present in HF, likely because of stimulation of juxtacapillary pulmonary receptors[54] or the rapidly adapting receptors in the proximal airways.[55] Progressive worsening of dyspnoea is more often likely to be attributed to increased severity of COPD rather than a complication of HF. A patient with known COPD presenting with acute onset dyspnoea is likely to be diagnosed as having AECOPD than acute LVF. In COPD, new onset orthopnoea or paroxysmal nocturnal dyspnoea, easy fatigability and reduced exercise tolerance in the absence of evidence of chest infection should arouse a suspicion of HF, especially if the patient also has additional risk factors for CAD. Of course, symptoms of angina will tilt the diagnosis in favour of CAD with HF. In acute onset dyspnoea, absence of cough or change in character of sputum should lead to a search for causes other than AECOPD, including acute LVF.

While the characteristic signs of COPD and HF are usually easy to recognise by an experienced clinician, combined presence of the two conditions can pose difficulties. Crackles may be heard in COPD due to opening of small airways and even wheeze is audible in HF due to airflow limitation in the smaller airways. Presence of a raised jugular venous pressure (JVP), tender enlarged liver and pedal oedema in COPD are more likely to be attributed to RV failure rather than overt LV failure. On the other hand, ambulatory patients with HF may not have any pulmonary signs. The crackles of pulmonary oedema may be inaudible in a hyperinflated chest. Pedal oedema alone is a poor marker of cardiac dysfunction. Presence of a loud P2 and left parasternal heave point towards cor-pulmonale while a pansystolic murmur over the mitral area may be due to a papillary muscle dysfunction in CAD. Again, a hyperinflated chest may mask cardiac sounds and murmurs.

In recent years, it has been increasingly recognised that LV diastolic dysfunction can also result in signs and symptoms of HF. The LV diastolic dysfunction is associated with increased mortality rates independent of systolic function. It is difficult to assess on the basis of clinical examination.

Chest Radiography

Classical radiological findings of HF are often modified in patients with COPD. Emphysema may cause atypical findings in pulmonary oedema. This is likely due to diffuse destruction of the pulmonary capillary bed. Vascular redistribution may be due to COPD rather than raised left arterial pressure (LAP). In acute LVF, pleural effusions may be absent and interstitial oedema (Kerley lines) may not be seen. Patients with long-standing elevations in PCWP often have significant remodelling of the blood vessels and alveolar-capillary membranes when exposed to chronically elevated pressures. These changes protect the lung from pulmonary oedema and cause the chest radiograph to be unreliable as an indicator of either

central haemodynamics or cardiac function.[56] Chest radiography is also less sensitive for detecting HF because the cardiothoracic ratio may remain in the normal range as the heart tends to become long and narrow ("tubular") in a hyperinflated chest. An RV enlargement may mask LV dilatation. Diastolic dysfunction cannot be diagnosed on chest radiography.

Figure 1 shows the chest radiograph of a patient with confirmed COPD who presented to the emergency with acute onset dyspnoea and was found to have LV enlargement with low ejection fraction as well as evidence of cor-pulmonale on echocardiography. It showed bilateral hyperinflated lung fields with flattened domes of diaphragm consistent with a diagnosis of AECOPD and a cardiothoracic ratio of 50 percent. Thus, cardiomegaly was masked.

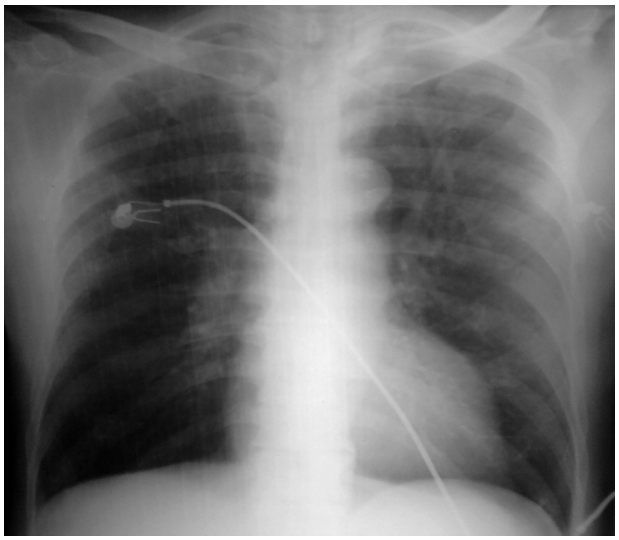

Figure 1. Chest radiograph of the patient with COPD presenting with acute LVF. ***For description, please see text.***

Electrocardiogram (ECG)

Many of the electrocardiographic abnormalities reported in COPD patients are similar to those seen in CAD with or without HF.[57] These include ST and T wave changes. The ST and T wave changes occur commonly in hypoxic COPD patients as do different types of arrythmias. The well known ECG features of right heart enlargement including a right axis devation, P-pulmonale, prominent R waves in right-sided chest leads and prominent S waves in left-sided chest leads are likely to mask LV changes. On the other hand, left-sided chamber hypertrophy and enlargement may alter or cancel out the above signs of right-sided enlargement. Hence, presence of mixed signs (for example, P-pulmonale with left axis deviation, P-pulmonale with left bundle branch block) or absence of the classical combination of features should arouse a suspicion on coexistent diseases. An ECG, however, provides little information on diastolic failure.

Figure 2 shows the ECG of the patient whose chest radiograph is shown above. Sinus tachycardia with normal axis, P-pulmonale, normal looking V1 and V2 leads with deep S-waves in V5, V6 were seen. Right axis deviation and R-waves in V1 that characterise RV hypertrophy were not found. Thus, the features are neither typical of right- nor left-sided enlargement.

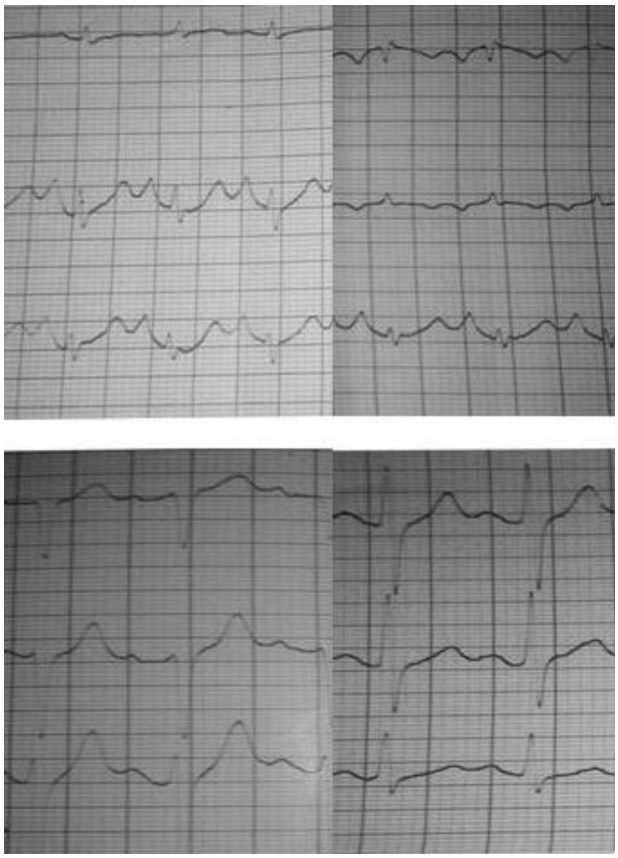

Figure 2. ECG of a patient with COPD presenting with acute LVF. ***Top left panel*****: Leads I, II, III;** ***Top right panel*****: Leads aVR, aVL, aVF;** ***Bottom left panel*****: Leads V1, V2, V3;** ***Bottom right panel*****: Leads V4, V56, V6.** ***For description, please see text.***

Pulmonary Function Tests (PFTs)

Post-bronchodilator airways obstruction is the physiological hallmark of COPD and as the disease progresses, the functional residual capacity (FRC) and residual volumes (RV) increase due to hyperinflation. Emphysema is recognised by an impairment of diffusion capacity. The HF has a mixed effect on pulmonary function. Due to pulmonary congestion, it tends to reduce lung volumes producing a restrictive element on PFT. Due to mucosal oedema in the smaller airways, there may be an impairment of airflows, especially at low lung volumes. Diffusion capacity

may be decreased in proportion to the loss of lung volume. There is no longitudinal study in patients with COPD who later developed HF to show how the latter modifies the PFT abnormalities of the former. However, opposing effects of COPD and HF on lung volumes and additive effects on airflow limitation can be expected. As airflow limitation is already present in COPD, complication with HF should tend to reduce the hyperinflation and decrease lung compliance.

In the example given above, spirometry revealed an FEV_1/FVC ratio of 0.5, FEV_1 of 1.01 L (29% of predicted) and FVC of 1.99 L (47% of predicted), pointing towards severe impairment of the lung function.

Echocardiography

Echocardiography is a valuable tool to study the structure and the function of the heart non-invasively and safely. Both the ventricles can be evaluated separately. The criteria for systolic and diastolic dysfunction are well established, and the low cost and easy availability make it an ideal tool to assess cardiac function in COPD, both in stable and acute exacerbations and determine the status of the LV when HF is coexistent with COPD. It is valuable to establish the diagnosis of diastolic dysfunction.[58] The diagnosis of diastolic HF is particularly difficult to establish in patients with COPD. The diagnosis of diastolic HF needs to be considered in COPD patients with LV ejection fraction >40% and abnormal LV mass or enlarged left atrium by echocardiography or impaired LV filling by radionucleide ventriculography (RNV).[39] Standard echocardiographic indices of LV diastolic dysfunction do not reliably permit the diagnosis of diastolic HF,[59] but the diagnosis can be established by comprehensive Doppler echocardiography and myocardial tissue imaging, which provide evidence for impaired myocardial relaxation (*i.e.*, decreased longitudinal velocity of the mitral annulus during early diastole and decreased propagation velocity mitral inflow), decreased LV compliance (shortened mitral A-wave duration and mitral deceleration time), and increased LV filling pressure (shortened isovolumic relaxation time and an increased ratio between early diastolic mitral and mitral annular velocities).[60]

Patients with COPD found to have an LV ejection fraction of <40% need to receive full HF therapy, including beta-adrenergic blockade. Patients with COPD with normal LV ejection fraction and normal LV mass or LV filling do not require HF therapy. However, echocardiographic windows can be limited by hyperinflated lungs and precise measurements may be difficult in upto a quarter of COPD patients.[61]

The echocardiography findings in the patient discussed above with ECG and chest radiograph shown in figures 1 and 2 revealed dilated left and right ventricles, dilated left and right atria, global hypokinesia, reduced LV systolic function (36%), severe diastolic dysfunction, *i.e.*, cor-pulmonale with dilated cardiomyopathy with poor LV compliance with severe systolic failure.

Cardiovascular Magnetic Resonance Imaging (CMR)

CMR is not affected by hyperinflated lungs. Moreover, visualisation and measurements of the RV are easier with CMR and RV function can be measured.[62] Easily assessable morphologic and volume-based CMR measurements have been shown to identify previously unknown left-sided CHF in mild to moderate COPD patients. Combination of CMR measurements of LV ejection fraction, indexed left- and right-atrial volume, and left ventricular end-systolic dimensions provided high added diagnostic value for identifying CHF. Left-sided measurements of CMR and echocardiography correlated well, including ejection fraction.[35] Disadvantages are the time-consuming data-acquisition and post-processing and the higher cost of CMR compared to echocardiography.[62]

Plasma Natriuretic Peptides (BNP)

In patients with HF, increased wall stretch due to volume and pressure overload leads to an increase in circulating natriuretic peptides (ANP and BNP and their N-terminal fragments NT-proANP and NT-proBNP). Plasma BNP levels: (normal: < 20pg/mL) are influenced by age, sex, and also by genetic factors. The ANP and BNP are synthesised and released by atrial and ventricular myocytes.[63] They can, however, not reliably discriminate between HF due to reduced ejection fraction and HF with preserved systolic function.

As a screening tool, B-type natriuretic peptide (BNP) plasma levels have proved to be very useful in evaluating the presence of HF in patients with AECOPD. Values of greater than 500pg/mL are highly suggestive of overt CHF. Values between 100 to 500 pg/mL are intermediate and should alert to the possible presence of HF complicating COPD and are an indication for treating the former until other investigations are done for confirmation. Such levels can be found in both RV and LV failure. After patients with AECOPD have stabilised and returned to the baseline, therapy for HF needs to be adjusted after cardiac imaging studies. Values less than 100pg/mL are usually sufficient to rule out overt HF.[39]

In a study to determine whether BNP can distinguish new-onset HF in patients with COPD or asthma presenting with dyspnoea to the emergency, McCullough *et al*[64] reported mean BNP values of 587pg/mL and 108.8pg/mL for those with and without HF. At a cut-point of 100 pg/mL, BNP had the following decision statistics: sensitivity 93.1%, specificity 77.3%, positive predictive value 51.9%, negative predictive value 97.7%, accuracy 80.6%, positive likelihood ratio 4.10, and negative likelihood ratio 0.09. If BNP would have been added to clinical judgment at a cut-point of 100pg/mL, 95% of the HF subjects would have been correctly diagnosed. Thus, adding routine BNP testing in patients with a history of asthma or COPD and presenting with acute dyspnoea yielded newly diagnosed HF in 20% patients that would have otherwise been overlooked.[64] Mueller *et al*[65] confirmed the clinical utility of BNP levels in pulmonary patients presenting with acute dyspnoea. Time to discharge and total cost of treatment were reduced with the use of BNP as compared to clinical evaluation alone, as it helped in decision-making on the coexistent HF. In differentiating between cardiac and respiratory causes of acute dyspnoea in pre-hospital emergency setting, NT-proBNP in combination with capnometry and clinical assessment was superior to NT-proBNP alone or NT-proBNP in combination with clinical assessment. The values of NT-proBNP≥2000pg/mL and $PetCO_2 \leq 4kPa$ were strong independent predictors for acute HF. In the group of acute HF dyspnoeic patients, subgroup of patients with previous COPD/asthma had significantly higher $PetCO_2$. In the group of COPD/asthma dyspnoeic patients, NT-proBNP was significantly higher in the subgroup of patients with previous HF.[66]

In ambulatory symptomatic and asymptomatic patients with chronic, stable systolic HF, plasma BNP levels ranging from 5 to 572pg/mL (median, 147pg/mL) have been reported. In upto 20% symptomatic patients, plasma BNP levels are below 100pg/mL.[67] In another study of hypertensive patients with systolic HF, the mean BNP (pmol/L) was 44.78.[68] Thus, the BNP levels lack sensitivity in the chronic compensated state. In patients with low BNP levels, echocardiography is a superior modality to uncover unsuspected LV systolic dysfunction in patients with stable COPD and RNV is an alternative when a poor acoustic window impedes evaluation by echocardiography in COPD patients.

THERAPEUTIC CHALLENGES

Effect of Drugs and Treatment for COPD on Cardiac Function

The major drug classes used in COPD include beta-adrenergic agonist bronchodilators (short-acting beta-agonists [SABAs] and long-acting beta agonists [LABAs]) and anticholinergics. Though largely β_2-adrenergic receptor stimulants, SABAs do stimulate β_1-receptors in the myocardium and regular use may lead to down regulation of these receptors with resultant increased myocardial oxygen consumption and endogenous catecholamine production.

It was shown that if a COPD patient is suffering from pre-existing cardiac arrhythmias and hypoxaemia, LABAs may have adverse effects on the myocardium.[69] In patients who have pre-existing CAD, LABAs increase the risk of non-fatal ischaemic events.[70] A recent meta-analysis of five single-dose and six longer-duration trials of β_2-agonists in COPD has suggested adverse cardiovascular effects of these drugs.[71] Treatment with β_2-agonists is associated with an increased risk for hospitalisation and all-cause mortality in patients with pre-existing HF.[72] Therefore, the adverse effects of β_2-agonists are likely to be aggravated in COPD patients with coexistent HF. Caution is advised on the use of these drugs in such a situation. Lowest possible doses of SABAs should be used, preferably by a metered dose inhaler or a dry powder system, on an as-needed basis. The LABAs will continue to be used until the question of their long-term safety is addressed in coexistent COPD-HF. The use of beta-blockers to counter the cardiotoxicity of β_2-agonists has not been investigated.

No short-term or long-term adverse cardiac effects have been noted with anticholinergics, either ipratropium or tiotropium, in patients with COPD with coexistent HF. However, corticosteroids do have the potential to cause water retention that can worsen HF as well as lead to metabolic complications, such as hypokalemia and metabolic alkalosis. Theo-phyllines are seldom used in COPD in most developed countries but are frequently prescribed in developing nations, including India, as a low cost, oral alternative to inhaled drugs. This is especially seen at primary and secondary care level as well as non-specialist level in tertiary care. Injectable theophyllines continue to be used for AECOPD. Theophyllines are cardiotoxic if serum levels exceed 20mg/L. Palpitations and arrythmias, especially multifocal atrial tachycardia and ectopics are commonly seen. These are even more likely when HF coexists and in acute LVF. Heart failure decreases elimination of theophylline. Hence, these drugs are best avoided in coexistent COPD-HF, both in stable patients and in those presenting with acute dyspnoea.

Oxygen is used for acute and chronic respiratory failure to maintain a saturation above 90% and with adequate haemoglobin, this ensures adequate tissue supply. The myocardium also benefits from this. Non-invasive ventilation is another modality that now defines the standard of care in AECOPD and would improve cardiac function if there is associated

HF. Patients with acute respiratory failure due to AECOPD may require mechanical ventilation. Cardiac adverse effects are even more likely when associated HF is there. Several aspects including the airway pressures, oxygenation, fluid and electrolyte balance, arrhythmias and cardiopulmonary haemodynamics require careful attention and monitoring.

Effects of Drugs for HF on COPD

Treatment options for HF include diuretics, β-blocking drugs, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARB), aldosterone antagonists and digitalis.

In coexistent COPD-HF, excessive diuresis can cause metabolic alkalosis that theoretically may inhibit ventilation. However, this is usually of little consequence as other treatments to increase ventilation are provided in AECOPD. Diuresis may actually improve gas exchange by removal of lung water and reduce work of breathing and dyspnoea by improving lung compliance and reduced pulmonary congestion.

The most debatable issue is the use of β-blockers when COPD is complicated by HF. The survival benefit conferred by β-blockers in systolic HF is well established.[73,74] Should the benefit of these drugs be denied to those HF patients who also have COPD?

Traditionally, these drugs have been considered as contraindicated in COPD even though the demonstrated detrimental effects were short-term effects on pulmonary function with non-selective agents.[75] The safety of β-blockers in COPD is well established.[76] A recent meta-analysis[77] has shown that cardioselective β-blocking drugs can be administered safely to COPD patients, even in those patients with some bronchospasm, with no or only small negative long-term effects on pulmonary function. Selective β_1 blockers do not antagonise the bronchodilator action of β_2-agonists.[78]

On evidence, selective β_1-blockers should not be withheld when COPD coexists with CVDs, because the benefits of selective blockade in such patients far outweigh the risks.[39] Yet, prescription practices indicate otherwise. There are wide variations in the prescriptions of β-blockers in coexistent COPD and HF. Cardiologists may be more likely to prescribe these drugs when the decisions are not made by a team including pulmonologists. In the study by Recio-Iglesias *et al*[50] at discharge, 27.6% of patients with HF and COPD received β-blockers. They observed that prescription of β-blockers was conditioned by LV ejection function, without relationship with severity of COPD. In another study, on discharge, patients with COPD-HF were less likely to receive β-blockers (12% *vs* 28%) and had a higher mortality. This was attributed to underutilisation of β-blockers.[49] Despite the overwhelming evidence supporting cardioselective β-blockade safety and tolerability in COPD patients, β-blockers are underprescribed to HF patients with concomitant COPD.[48] In a study in primary care settings, only 18% of patients with a combined diagnosis of COPD and HF received β-blockers.[51]

Le Jemtel *et al*[39] have summarised the current status and consensus on the use of β-blockers in COPD. Selective β_1-adrenergic blockade is indicated in all HF patients with concomitant stable COPD. However, this may be temporarily stopped during AECOPD until safety data is available.

The ACE inhibition and antagonism of angiotensin-II is the cornerstone of treatment of HF. Angiotensin-II is a potent pulmonary airway constrictor. Therefore, ACE inhibitors and ARBs carry a potential benefit in coexistent COPD by decreasing angiotensin-II levels or antagonising it, and thus, reduce airways obstruction as well as prevent lung injury. Other putative benefits may be there as they can also decrease pulmonary inflammation and pulmonary vascular constriction[79-81] and improve the alveolar membrane gas exchange.[82] However, these suggested benefits remain to be demonstrated in coexistent COPD-HF. Even in patients with COPD without CVDs, and in those with PH, exercise capacity or dyspnoea score are not improved.[83,84] The ACE inhibition in COPD does not increase dry cough, which if present should actually alert to the presence of HF.[85]

Aldosterone can damage the alveolar-capillary membrane.[86] Aldosterone antagonists, such as spironolactone, may offer a protection. Digitalis may, however, reduce lung function because it can cause pulmonary vasoconstriction and being an inhibitor of sodium-potassium adenosine triphosphatase inhibitor has the potential to increase airways obstruction. These effects too have not been documented in any clinical studies. Caution is, however, advised with such drugs in coexistent COPD-HF that have the potential to worsen airway function.

Statins are now among the most widely used drugs all over the world, indicated in the treatment of dyslipidemia and metabolic syndrome as well as established atherosclerotic CVD. The recent discovery of their potent anti-inflammatory properties and role in improving the endothelial cell function, further makes them ideal drugs for the co-morbidities associated with COPD, especially HF and CAD. There is enough evidence that statins may cause regression of the atherosclerotic lesions of CAD.[87] However, the role of statins in HF has been a controversial domain considering the available experimental data indicating both beneficial and harmful effects. Not high, but low levels of cholesterol are related to

increased mortality.[88] Cholesterol reduction by statins *per se* may prove detrimental in patients with HF, as cholesterol seems to be able to inactivate endotoxin as a stimulus for pro-inflammatory cytokine production.[89]

On the other hand, statins have also been found to reduce the decline in pulmonary function in COPD as well as protect against the development of lung cancer.[90,91] Human menopausal gonadotropin-CoA reductase inhibition with simvastatin inhibits development of emphysema, inflammation, and PH in animal models of smoking-induced lung injury[92] and reverses PH in animal model of toxic injury to the pulmonary vasculature.[93] There have been no clinical trials to address the benefits and harmful effects in a population with coexistent COPD and HF. However, presence of dyslipidemia and CAD is sufficient indication for using these drugs.

CONCLUSIONS

There are several unresolved and debatable issues in managing patients who have both COPD and HF. From a pulmonologist's point of view, occurrence of HF on pre-existing COPD is very frequent and more so in acute presentations of dyspnoea. In the latter event, a previously asymptomatic HF may manifest for the first time. Therefore, awareness of co-occurrence is essential and a high index of suspicion should be maintained. Active search for evidence of HF using clinical examination supplemented with specialised investigations including plasma natriuretic peptides and echocardiography should be carried out followed by appropriate management. While BNP is extremely useful in differential diagnosis in acute dyspnoea, echocardiography is the more definitive modality to diagnose HF in stable COPD. The prognosis of coexistent COPD and HF is poorer.

For the cardiologist too, awareness of this very frequent co-occurrence is as important as the outcomes of interventions may be affected. Chronic obstructive pulmonary disease increases the peri-operative morbidity and mortality due to cardiac surgery. A symptom like dyspnoea due to COPD is not likely to respond if it is wrongly attributed to HF and treated as such, and that due to HF will also not respond if treated like a case with COPD. Issues, such as adverse effects of drugs on cardiac or pulmonary function need to be sorted out by studies in coexistent COPD-HF patients. Caution is advised with the use of β_2-agonists in COPD when HF is also present, more so in acute exacerbations. On current evidence, the beneficial effects of selective β_1-blockers should not be denied to stable patients who have coexistent COPD-HF. As two major systems are involved and there are debatable issues in management, a team approach is required for optimal management.

REFERENCES

1. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance: United States, 1971-2000. *MMWR Surveill Summ* 2002;51:1-16.
2. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance—United States, 1971-2000. *Respir Care* 2002;47:1184-99.
3. Chen JC, Mannino DM. Worldwide epidemiology of chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 1999;5:93-9.
4. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 1997;349:1436-42.
5. McCullough PA, Philbin EF, Spertus JA, Kaatz S, Sandberg KR, Weaver WD; Resource Utilization Among Congestive Heart Failure (REACH) Study. Confirmation of a heart failure epidemic: findings from the Resource Utilization Among Congestive Heart Failure (REACH) study. *J Am Coll Cardiol* 2002;39:60-9.
6. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure. *Part I*. Diagnosis, prognosis, and measurements of diastolic function. *Circulation* 2002;105:1387-93.
7. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, *et al*. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation* 2002;106:3068-72.
8. Rutten FH, Cramer MM, Lammers JJ, Grobbee DE, Hoes AW. Heart failure and chronic obstructive pulmonary disease: an ignored combination. *Eur J Heart Fail* 2006;8:706-11.
9. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for diagnosis, management and prevention of COPD. **U**pdate 2009. *Available at* www.goldcopd.org
10. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, *et al.* The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005). *Eur Heart J* 2005;26:1115-40.
11. Hatano S, Strasser T. Primary pulmonary hypertension. Report on a WHO Meeting. Geneva: World Health Organization; 1975:pp7-45.
12. Hansell AL, Walk JA, Soriano JB. What do chronic obstructive pulmonary disease patients die from? A multiple cause coding analysis. *Eur Respir J* 2003;22: 809-14.
13. Mannino DM, Brown C, Giovino GA. Obstructive lung disease deaths in the United States from 1979 through 1993. *Am J Respir Crit Care Med* 1997;156:814-8.
14. Anthonisen NR, Connett JE, Enright PL, Manfreda J. Lung Health Study Research Group. Hospitalizations and mortality in the Lung Health Study. *Am J Respir Crit Care Med* 2002;166:333-9.
15. Zvezdin B, Milutinov S, Kojicic M, Hadnadjev M, Hromis S, Markovic M, *et al*. A postmortem analysis of major causes of early death in patients hospitalized with COPD exacerbation. *Chest* 2009;136:376-80.
16. Maclay JD, Mcallister DA, Macnee W. Cardiovascular risk in chronic obstructive pulmonary disease. *Respirology* 2007;12:634-41.
17. Sin DD, Paul Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc* 2005;2:8-11.
18. Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. *Chest* 2005;128:2640-6.

19. Sin DD, Hogg J. Are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular morbidity and mortality? *CVR&R* 2004;25:168-70.
20. Tukek T, Yildiz P, Atilgan D, Tuzcu V, Eren M, Erk O, *et al.* Effect of diurnal variability of heart rate on development of arrhythmia in patients with chronic obstructive pulmonary disease. *Int J Cardiol* 2003;88:199-206.
21. Horton R. The neglected epidemic of chronic disease. *Lancet* 2005;366:1514.
22. U.S. Surgeon General. The health consequences of smoking: a report of the Surgeon general, Washington D.C. Department of Health and Human Services. Centres of Disease Control and Prevention, National Centre for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004.
23. Sin DD, Paul Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003;107:1514-9.
24. de Torres JP, Cordoba-Lanus E, Lopez-Aguilar C, de Fuentes MM, de Garcini AM, Aguirre-Jaime A, *et al*. C-reactive protein levels and clinically important predictive outcomes in stable COPD patients. *Eur Respir J* 2006;27:902-7.
25. Pinto-Plata VM, Mullerova H, Toso JF, Feudjo-Tepie M, Soriano JB, Vessey RS, *et al*. C-reactive protein in patients with COPD, control smokers and non-smokers. *Thorax* 2006;61:23-8.
26. Harrison D, Griendling KK, Landmesser U, Hornig B, Drexler H. Role of oxidative stress in atherosclerosis. *Am J Cardiol* 2003;91:7A-11A.
27. Nadeem A, Raj HG, Chhabra SK. Increased oxidative stress and altered levels of antioxidants in chronic obstructive pulmonary disease. *Inflammation* 2005;29:23-32.
28. Chhabra SK. Pulmonary hypertension associated with chronic obstructive pulmonary disease. *Indian J Chest Dis Allied Sci* 2010;52:29-40.
29. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, *et al*. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009;54:43-54.
30. Vonk-Noordegraaf A, Marcus JT, Holverda S, Roseboom B, Postmus PE. Early changes of cardiac structure and function in COPD patients with mild hypoxemia. *Chest* 2005;127:1898-1903.
31. Sciurba FC, Rogers RM, Keenan RJ, Slivka WA, Gorcsan J 3rd, Ferson PF, *et al*. Improvement in pulmonary function and elastic recoil after lung-reduction surgery for diffuse emphysema. *N Engl J Med* 1996;334:1095-9.
32. Jörgensen K, Houltz E, Westfelt U, Nilsson F, Scherstén H, Ricksten SE. Effects of lung volume reduction surgery on left ventricular diastolic filling and dimensions in patients with severe emphysema. *Chest* 2003;124:1863-70.
33. Iversen KK, Kjaergaard J, Akkan D, Kober L, Torp-Pedersen C, Hassager C, *et al*. Chronic obstructive pulmonary disease in patients admitted with heart failure. *J Intern Med* 2008;264:361-9.
34. Vonk Noordegraaf A, Marcus JT, Roseboom B, Postmus PE, Faes TJ, de Vries PM. The effect of right ventricular hypertrophy on left ventricular ejection fraction in pulmonary emphysema. *Chest* 1997;112:640-5.
35. Rutten FH, Vonken EJ, Cramer MJ, Moons KG, Velthuis BB, Prakken NH, *et al*. Cardiovascular magnetic resonance imaging to identify left-sided chronic heart failure in stable patients with chronic obstructive pulmonary disease. *Am Heart J* 2008;156:506-12.
36. Barr RG, Bluemke DA, Ahmed FA. Percent emphysema, airflow obstruction, and impaired left ventricular filling. *N Engl J Med* 2010;362:217-27.
37. Rennard SI. Clinical approach to patients with chronic obstructive pulmonary disease and cardiovascular disease. *Proc Am Thorac Soc* 2005;2:94-100.
38. Ramani GV, Uber PA, Mehra MR. Chronic heart failure: contemporary diagnosis and management. *Mayo Clin Proc* 2010;85:180-95.
39. Le Jemtel TH, Padeletti M, Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol* 2007;49:171-80.
40. Curkendall SM, DeLuise C, Jones JK, Lanes S, Stang MR, Goehring E Jr, *et al*. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. *Ann Epidemiol* 2006;16:63-70.
41. Holguin F, Folch E, Redd SC, Mannino DM. Co-morbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. *Chest* 2005;128:2005-11.
42. Sidney S, Sorel M, Quesenberry CP Jr, DeLuise C, Lanes S, Eisner MD. COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest* 2005;128:2068-75.
43. McCollough PA. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. *Acad Emerg Med* 2003;10:198-204.
44. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, *et al*. Euro Heart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006;27:2725-36.
45. Funk GC, Lang I, Schenk P, Valipour A, Hartl S, Burghuber OC. Left ventricular diastolic dysfunction in patients with COPD in the presence and absence of elevated pulmonary arterial pressure. *Chest* 2008;133:1354-9.
46. Havranek EP, Masoudi FA, Westfall KA, Wolfe P, Ordin DL, Krumholz HM. Spectrum of heart failure in older patients: results from the National Heart Failure project. *Am Heart J* 2002;143:412-7.
47. Dahlström U. Frequent non-cardiac comorbidities in patients with chronic heart failure. *Eur J Heart Fail* 2005;7:309-16.
48. Mascarenhas J, Lourenço P, Lopes R, Azevedo A, Bettencourt P. Chronic obstructive pulmonary disease in heart failure: prevalence, therapeutic and prognostic implications. *Am Heart J* 2008;155:521-5.
49. Lainscak M, Hodoscek LM, Düngen HD, Rauchhaus M, Doehner W, Anker SD, *et al*. The burden of chronic obstructive pulmonary disease in patients hospitalized with heart failure. *Wien Klin Wochenschr* 2009;121:309-13.
50. Recio-Iglesias J, Grau-Amorós J, Formiga F, Camafort-Babkowski M, Trullàs-Vila JC, Rodríguez A, *et al*. Chronic obstructive pulmonary disease on inpatients with heart failure. GESAIC study results. *Med Clin* (Barc) 2010; 134:427-32.
51. Hawkins NM, Jhund PS, Simpson CR, Petrie MC, Macdonald MR, Dunn FG, *et al*. Primary care burden and treatment of patients with heart failure and chronic obstructive pulmonary disease in Scotland. *Eur J Heart Fail* 2010;12:17-24.
52. Mascarenhas J, Azevedo A, Bettencourt P. Coexisting chronic obstructive pulmonary disease and heart failure: implications for treatment, course and mortality. *Curr Opin Pulm Med* 2010;16:106-11.
53. De Blois J, Simard S, Atar D, Agewall S; Norwegian Heart Failure Registry. COPD predicts mortality in HF: the Norwegian Heart Failure Registry. *J Card Fail* 2010;16: 225-9.

54. Paintal AS. Impulses in vagal afferent fibres form specific pulmonary deflation receptors. The response of these receptors to phenyl diguanide, potato starch, 5-hydroxytryptamine and nicotine, and their role in respiratory and cardiovascular reflexes. *Quart J Exp Physiol* 1955;40:89-111.
55. Ravi K, Kappagoda TS. Rapidly adapting receptors in acute heart failure and their impact on dyspnoea. *Respir Physiol Neurobiol* 2009;167:107-15.
56. Gehlbach BK, Geppert E. The Pulmonary manifestations of left heart failure. *Chest* 2004;125:669-82.
57. Harrigan RA, Jones K. ABC of clinical electrocardiography: conditions affecting the right side of the heart. *BMJ* 2002;324:1201-4.
58. Poulsen SH. Clinical aspects of left ventricular diastolic function assessed by Doppler echocardiography following acute myocardial infarction. *Danish Med Bull* 2001;48: 199-210.
59. Petrie MC, Hogg K, Caruana L, McMurray JJ. Poor concordance of commonly used echocardiographic measures of left ventricular diastolic function in patients with suspected heart failure but preserved systolic function: is there a reliable echocardiographic measure of diastolic dysfunction? *Heart* 2004;90:511-7.
60. Oh JK, Hatle L, Tajik J, Little W. Diastolic heart failure can be diagnosed by comprehensive two-dimensional and Doppler echocardiography. *J Am Coll Cardiol* 2006;47:500-6.
61. Boussuges A, Pinet C, Molenat F, Burnet H, Ambrosi P, Badier M, *et al*. Left atrial and ventricular filling in chronic obstructive pulmonary disease. An echocardiographic and Doppler study. *Am J Respir Crit Care Med* 2000;162:670-5.
62. Pennell DJ, Sechtem UP, Higgins CB, Manning WJ, Pohost GM, Rademakers FE, *et al*. Clinical indications for cardiovascular magnetic resonance (CMR): consensus panel report. *Eur Heart J* 2004;25:1940-65.
63. Angermann CE, Ertl G. Natriuretic peptides—new diagnostic markers in heart disease. *Herz* 2004;29:609-17.
64. McCullough PA, Hollander JE, Nowak RM, Storrow AB, Duc P, Omland T, *et al*. Uncovering heart failure in patients with a history of pulmonary disease: rationale for the early use of B-type natriuretic peptide in the emergency department. *Acad Emerg Med* 2003;10:198-204.
65. Mueller C, Laule-Kilian K, Frana B, Rodriguez D, Scholer A, Schindler C, *et al*. Use of B-type natriuretic peptide in the management of acute dyspnea in patients with pulmonary disease. *Am Heart J* 2006;151:471-7.
66. Klemen P, Golub M, Grmec S. Combination of quantitative capnometry, N-terminal pro-brain natriuretic peptide, and clinical assessment in differentiating acute heart failure from pulmonary disease as cause of acute dyspnea in pre-hospital emergency setting: study of diagnostic accuracy. *Croat Med J* 2009;50:133-42.
67. Tang WH, Girod JP, Lee MJ, Starling RC, Young JB, Van Lente F, *et al*. Plasma B-type natriuretic peptide levels in ambulatory patients with established chronic symptomatic systolic heart failure. *Circulation* 2003;108:2964-66.
68. Falcão LM, Pinto F, Ravara L, van Zwieten PA. BNP and ANP as diagnostic and predictive markers in heart failure with left ventricular systolic dysfunction. *J Renin Angiotensin Aldosterone Syst* 2004;5:121-9.
69. Cazzola M, Imperatore F, Salzillo A, Di Perna F, Calderaro F, Imperatore A, *et al*. Cardiac effects of formoterol and salmeterol in patients suffering from COPD with preexisting cardiac arrhythmias and hypoxemia. *Chest* 1998;114:411-5.
70. Martin RM, Dunn NR, Freemantle SN, Mann RD. Risk of nonfatal cardiac failure and ischaemic heart disease with long acting beta 2 agonists. *Thorax* 1998;53:558-62.
71. Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. *Chest* 2004;125:2309-21.
72. Au DH, Udris EM, Fan VS, Curtis JR, McDonell MB, Fihn SD. Risk of mortality and heart failure exacerbations associated with inhaled beta-adrenoceptor agonists among patients with known left ventricular systolic dysfunction. *Chest* 2003;123:1964-9.
73. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, *et al*. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. US Carvedilol Heart Failure Study Group. *N Engl J Med* 1996;334:1349-55.
74. The MERIT-HF Investigators. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001-7.
75. Gheorghiade M, Colucci WS, Swedberg K. Beta-blockers in chronic heart failure. *Circulation* 2003;107:1570-5.
76. George RB, Manocha K, Burford JG, Conrad SA, Kinasewitz GT. Effects of labetalol in hypertensive patients with chronic obstructive pulmonary disease. *Chest* 1983;83:457-60.
77. Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective beta-blockers in patients with reactive airway disease: a meta-analysis. *Ann Intern Med* 2002;137:715-25.
78. van der Woude HJ, Zaagsma J, Postma DS, Winter TH, van Hulst M, Aalbers R. Detrimental effects of beta-blockers in COPD: a concern for nonselective beta-blockers. *Chest* 2005;127:818-24.
79. Mancini GB. The "double dip" hypothesis: simultaneous prevention of cardiovascular and pulmonary morbidity and mortality using angiotensin II type 1 receptor blockers. *Can J Cardiol* 2005;21:519-23.
80. Kuba K, Imai Y, Penninger JM. Angiotensin-converting enzyme 2 in lung diseases. *Curr Opin Pharmacol* 2006;6:271-6.
81. Forth R, Montgomery H. ACE in COPD: a therapeutic target? *Thorax* 2003;58:556-8.
82. Guazzi M. Alveolar-capillary membrane dysfunction in heart failure:evidence of a pathophysiologic role. *Chest* 2003;124:1090-102.
83. Morrell NW, Higham MA, Phillips PG, Shakur BH, Robinson PJ, Beddoes RJ. Pilot study of losartan for pulmonary hypertension in chronic obstructive pulmonary disease. *Respir Res* 2005;6:88.
84. Andreas S, Herrmann-Lingen C, Raupach T, Lüthje L, Fabricius JA, Hruska N, *et al*. Angiotensin II blockers in obstructive pulmonary disease: a randomised controlled trial. *Eur Respir J* 2006;27:972-9.
85. Packard KA, Wurdeman RL, Arouni AJ. ACE inhibitor-induced bronchial reactivity in patients with respiratory dysfunction. *Ann Pharmacother* 2002;36:1058-67.
86. Agostoni P, Magini A, Andreini D, Contini M, Apostolo A, Bussotti M, *et al*. Spironolactone improves lung diffusion in chronic heart failure. *Eur Heart J* 2005;26:159-64.
87. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantigne CM, *et al*. Effect of very high-intensity statin therapy on regression of Coronary Atherosclerosis: the Asteroid TRIAL. *JAMA* 2006;295:1556-65.
88. Van der HP, Voors AA, VanGilst WH, Bohm M, VanVeldhuiran DJ. Statin in the treatment of chronic heart failure: biological and clinical considerations. *Cardiovasc Res* 2006;71:443-54.
89. von Haehling S, Okonko DO, Anker SD. Statins: a treatment option for chronic heart failure? *Heart Fail Monit* 2004;4:90-7.

90. Khurana V, Bijjanki HR, Caldito G, Owens HW. Statins reduce the risk of lung cancer in humans: large case-control study of US veterans. *Chest* 2007;131:1282-8.
91. Alexeff SE, Litonjua AA, Sparrow D, Vokonas PS, Schwartz J. Statin use reduces decline in lung function: VA normative ageing study. *Am J Respir Crit Care Med* 2007;176:742-7.
92. Lee JH, Lee DS, Kim EK, Choe KH, Oh YM, Shim TS, *et al*. Simvastatin inhibits cigarette smoking-induced emphysema and pulmonary hypertension in rat lungs. *Am J Respir Crit Care Med* 2005;172:987-93.
93. Nishimura T, Vaszar LT, Faul JL, Zhao G, Berry GJ, Shi L, *et al*. Simvastatin rescues rats from fatal pulmonary hypertension by inducing apoptosis of neointimal smooth muscle cells. *Circulation* 2003;108:1640-5.