Cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease

Martin I MacDonald, Eskandarain Shafuddin*, Paul T King, Catherina L Chang, Philip G Bardin, Robert J Hancox*

Lancet Respir Med 2016; 4: 138–48

Published Online January 15, 2016 http://dx.doi.org/10.1016/S2213-2600(15)00509-3

*These authors contributed equally to this work

Monash Lung & Sleep, Monash Medical Centre, Monash University, Melbourne, VIC, Australia (M I MacDonald MBChB, P T King Phd, Prof P G Bardin PhD); **Department of Respiratory Medicine, Waikato Hospital, Hamilton, New Zealand** (E Shafuddin MBBS, C L Chang MD, R J Hancox MD); **and Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand** (E Shafuddin, R J Hancox)

Correspondence to: Dr Martin I MacDonald, Monash Lung & Sleep, Monash Medical Centre, 246 Clayton Road, Clayton, Melbourne, VIC 3168, Australia **martin.macdonald@monashhealth.org**

See Online for appendix

Chronic obstructive pulmonary disease (COPD) and cardiovascular disease often coexist, and acute cardiac events frequently occur during COPD exacerbations. Even when cardiac complications are not clinically apparent, biochemical evidence of cardiac dysfunction is often noted during exacerbations and portends poor prognosis. Diagnosis of cardiac disease in COPD can be difficult and necessitates a high degree of clinical suspicion. However, the additional strain of an exacerbation could be a pivotal moment, during which previously unsuspected cardiac dysfunction is exposed. In this Review, we present evidence about cardiac involvement in exacerbations of COPD, and discuss diagnostic challenges and treatment opportunities.

Introduction

Patients with chronic obstructive pulmonary disease (COPD) often have cardiovascular comorbidities.[1] Patients with cardiovascular complications tend to have more symptoms and higher mortality than do patients with COPD alone.[2] To distinguish symptoms of cardiac disease from those of COPD can be difficult, however, and cardiac disease is often unrecognised.[3,4] Exacerbations of COPD are characterised by symptomatic deterioration or increased use of health care; definitions do not ascribe cause, and primary cardiovascular instability precipitating acute deterioration in COPD symptoms is probably common.[3] At one extreme, decompensated cardiac failure could be mistaken for COPD exacerbation.[3,5] But even without clinical signs of cardiac involvement, biochemical evidence of cardiac dysfunction is often present.[6–19] Increased cardiac biomarkers during COPD exacerbations are associated with poor prognosis, but their wider implications are uncertain.[6,18,19] In this Review, we examine the evidence for cardiac dysfunction during exacerbations of COPD and provide diagnostic, prognostic, and therapeutic perspectives.

Key messages

- Diagnosed cardiac comorbidities are common in patients with chronic obstructive pulmonary disease (COPD) and are associated with worse outlook. Prevalence might be underestimated because of underdiagnosis.
- COPD exacerbations are often complicated by acute cardiac dysfunction, which can be difficult to recognise clinically.
- Biochemical evidence of myocardial stretch (B-type natriuretic peptides) and myocardial injury (troponins) is often noted in exacerbations of COPD and is associated with increased mortality.
- Results of observational studies suggest that cardiac treatments could improve outcomes from COPD exacerbations, but no prospective controlled trials have been done.
- Further research into the pathogenesis and treatment of acute cardiac dysfunction in COPD exacerbations is urgently needed.

Epidemiology

COPD can be an important comorbidity in patients with cardiovascular disease: it is identified in 7–16% of patients with acute myocardial infarction and up to 52% of patients with heart failure (appendix). The presence of COPD is associated with an increased risk of readmission to hospital and long-term mortality.[20] Patients with comorbid cardiac disease and COPD are less likely to be given β blockers for cardiac dysfunction or β agonists for airflow obstruction.[21,22]

About 20% of patients with COPD have a diagnosed cardiovascular comorbidity (appendix). Cardiovascular diagnoses are more common in those with severe airflow obstruction. Both airflow obstruction and low forced vital capacities are established cardiovascular risk factors,[23,24] and the results of population-based studies show at least a 30% higher risk of cardiovascular death in patients with impaired lung function, even after adjustment for age, smoking status, and traditional cardiovascular risk factors.[23–25] Accurate estimation of cardiovascular mortality in COPD is difficult, however, because death certificates can be unreliable. When cause of death is meticulously reviewed, cardiovascular disease (including cerebrovascular disease) seems to account for 25% of all-cause mortality.[26] Cardiac deaths outnumber respiratory deaths in mild and moderate COPD—only in advanced disease does respiratory failure predominate.[25] Comorbid heart failure in COPD is associated with a doubling of the mortality rate, poor quality of life, and low exercise tolerance.[27–29]

Cardiovascular disease can be detected in as many as 55% of patients admitted with exacerbations of COPD (table 1). Furthermore, around 20% of exacerbations of COPD could be due to acute decompensated heart failure and cardiac arrhythmias.[38] Comorbid cardiac failure, ischaemic heart disease, and arrhythmias have all been associated with reduced survival from exacerbations of COPD (table 1), and particularly with early inpatient mortality.[36,38,39] Retrospective studies have shown that 8–25% of patients with exacerbations of COPD have

	Study type	Population (n)	Key findings
Agabiti et al, 2010[30]	Retrospective cohort	Patients admitted to hospital (12 756)	Past history of IHD (15% of population; RR 1·3 [95% CI 1·1–1·5]), heart failure (10%; 1·7 [1·4–2·0]), and atrial fibrillation (11%; 1·2 [1·0–1·4]) predicted mortality at 30 days
Almagro et al, 2002[31]	Prospective cohort	Patients admitted to hospital (135)	Past history of heart failure (33% of population) predicted long-term (>2 years) mortality (OR 2·30 [95% CI 1·39–2·83])
Almagro et al, 2015[32]	Prospective cohort	Patients admitted to hospital (606)	Past history of IHD (21% of population; HR 1·29 [95% CI 1·04–1·61]), heart failure (33%; 2·31 [1·05–5·1]), and atrial fibrillation (21%; 2·8 [1·28–6·15]) predicted mortality at 3 months
Brekke et al, 2008[33]	Retrospective cohort	Patients admitted to hospital (897)	Past history of IHD (29% of population; HR 1·54 [95% CI 1·05–2·26]) and current atrial fibrillation (10%; 1·4 [1·03–1·9]) predicted mortality at 2 years, past history of heart failure (10%; 1·26 [0·91–1·75]) did not
Bustamante-Fermosel et al, 2007[34]	Retrospective cohort	Patients admitted to hospital (972)	Current heart failure (28% of population) predicted in-hospital mortality (RR 3·47 [95% CI 1·24–9·66])
Chang et al, 2011[35]	Prospective cohort	Patients admitted to hospital (250)	Past history of cardiac disease (30% of population) did not predict mortality at 30 days (OR 0·7 [95% CI 0·25–1·99])
Connors et al, 1996[5]	Prospective cohort	Patients admitted to hospital (1016)	Current heart failure (26% of population; HR 0·66 [95% CI 0·45–0·97]) predicted mortality at 6 months, past history of any cardiac disease did not (1·06 [0·74–1·5])
Dransfield et al, 2008[36]	Retrospective cohort	Patients admitted to hospital (825)	Past history of heart failure (28% of population) predicted in-hospital mortality (OR 4·54 [95% CI 1·53–13·5])
Escande et al, 2014[37]	Prospective cohort	Patients admitted to hospital (29)	Current heart failure (52% of population) predicted mortality at 5 years (HR 3·37 [95% CI 1·19–9·56])
Fruchter et al, 2009[37]	Retrospective cohort	Patients admitted to hospital (182)	Past history of IHD (43% of population) predicted mortality at 3 years (HR 2·34 [95% CI 1·38–3·95])
Fuso et al, 1995[38]	Retrospective cohort	Patients admitted to hospital (590)	Cardiac arrhythmia (19% of population; OR 1·91 [95% CI 1·10–3·31]) and current atrial fibrillation (8%; 2·27 [1·14–4·51]) predicted in-hospital mortality, past history of IHD (3%; 2·69 [0·91–7·97]) did not
Harrison et al, 2014[39]	Prospective cohort	Patients admitted to hospital (1343)	Past history of heart failure (proportion of participants with heart failure not reported) predicted in-hospital mortality (OR 1·75 [95% CI 1·06–2·91]) and mortality at 1 year (1·52 [1·11–21])
Hasegawa et al, 2014[40]	Retrospective cohort	Patients admitted to hospital (177 207)	Past history of heart failure (18% of population) predicted in-hospital mortality (OR 1·31 [95% CI 1·23–1·40])
Incalzi et al, 1997[41]	Prospective cohort	Patients admitted to hospital (270)	Current IHD (6% of population; HR 1·42 [95% CI 1·02–1·96]) predicted mortality at 5 years, past history of IHD (4%; 1·05 [0·54–2·05]) did not
Lainscak et al, 2011[42]	Retrospective cohort	Patients admitted to hospital (968)	Past history of heart failure (27% of population) predicted mortality at 4 years (HR 1·72 [95% CI 1·39–2·14])
Lindenauer et al, 2013[43]	Retrospective cohort	Patients admitted to hospital (150 035)	Past history of heart failure (42% of population; OR 1·34 [95% CI 1·28–1·39]) and atrial fibrillation (37%; 1·17 [1·12–1·22]) predicted mortality at 30 days; past history of IHD (50%; 0·87 [0·83–0·90]) did not
Marcun et al, 2012[44]	Prospective cohort	Patients admitted to hospital (127)	Current heart failure (55% of population) did not predict mortality at 6 months (HR 0·97 [95% CI 0·23–3·97])
McGhan et al, 2007[45]	Retrospective cohort	Patients admitted to hospital (51353)	Past history of heart failure (20% of population) predicted mortality at 5 years (HR 1·36 [95% CI 1·32–1·40])
Raurich et al, 2004[46]	Retrospective cohort	Patients admitted to intensive-care unit (101)	Past history of IHD (16% of population; RR 1·0 [95% CI 0·4–2·4]) and heart failure (15%; 1·7 [0·8–3·6]) did not predict in-hospital mortality
Roberts et al, 2011[47]	Retrospective cohort	Patients admitted to hospital (9201)	History of atrial fibrillation (10% of population) predicted in-hospital mortality (RR 1·31 [95% CI 1·05–1·62]) and mortality at 3 months (1·35 [1·17–1·55]), past history of heart failure (7%) predicted mortality at 3 months (1·61 [1·37–1·89]). Past history of IHD (25%) did not predict in-hospital mortality (0·98 [0·83–1·16]) or mortality at 3 months (0·96 [0·85–1·08])
Slenter et al, 2013[48]	Retrospective cohort	Patients admitted to hospital (260)	Past history of heart failure (22% of population) predicted mortality at 1 year (HR 1·75 [95% CI 1·03–2·97])
Soyseth et al, 2007[49]	Retrospective cohort	Patients admitted to hospital (854)	Past history of IHD (29% of population; 1·3 [95% CI 1·0–1·7]), heart failure (20%; 1·6 [1·2–2·2]), and atrial fibrillation (20%; 1·6 [1·2–2·1]) predicted mortality at 2 years
Steer et al, 2012[50]	Prospective cohort	Patients admitted to hospital (920)	Current atrial fibrillation (13% of population) predicted in-hospital mortality (OR 2·66 [95% CI 1·39–5·09])
Stiell et al, 2014[51]	Prospective cohort	Patients admitted to hospital (945)	Neither past history of IHD (11% of population; OR 2·03 [95% CI 0·84–4·92]), current IHD (1%; 3·25 [0·95–11·04]), nor current heart failure (10%; 1·88 [0·94–3·78]) predicted mortality at 30 days
Tabak et al, 2013[52]	Retrospective cohort	Patients admitted to hospital (102 626)	Past history of heart failure (28% of population) predicted in-hospital mortality (OR 1·46 [95% CI 1·33–1·61])
Terzano et al, 2010[53]	Prospective cohort	Patients admitted to hospital (288)	Past history of IHD (16% of population) predicted mortality at 7 years (HR 3·43 [95% CI 1·02–11·55])
Wildman et al, 2009[54]	Prospective cohort	Patients admitted to intensive-care unit (832*)	Current atrial fibrillation (12% of population) did not predict mortality at 6 months (OR 1·58 [95% CI 0·98–2·54])

IHD=ischaemic heart disease. RR=risk ratio. OR=odds ratio. HR=hazard ratio. *Of these 832 patients, 752 had exacerbations of chronic obstructive pulmonary disease, and 80 had asthma exacerbations.

***Table 1*: Studies of prevalence of cardiac disease and association with mortality in exacerbations of chronic obstructive pulmonary disease**

abnormal cardiac troponin concentrations and electrocardiograms, fulfilling diagnostic criteria for acute coronary syndromes.[4,7] Only a small proportion of these events are recognised in routine clinical practice.[4,8]

Evidence for cardiac dysfunction in exacerbations

Cardiac muscle injury

Biochemical evidence of cardiac injury during COPD exacerbations is common (table 2) and predicts both short-term and long-term mortality.[6] Troponins are globular protein complexes bound to the actin filaments of myocytes that regulate contraction of skeletal and cardiac muscle. These proteins are released into the peripheral blood from cardiomyocytes after myocardial injury. Troponin measurements are mainly used to diagnose acute myocardial infarction, but, although they are specific for myocardial necrosis, they are not specific for ischaemic injury because cardiac troponins can also be raised in heart failure, renal dysfunction, pulmonary embolism, pulmonary hypertension, tachyarrhythmias, and sepsis. Although increased cardiac troponin concentrations in these disorders do not necessarily suggest an acute coronary syndrome, they are nonetheless consistently associated with poor prognosis.[70]

In patients with stable COPD, baseline concentrations of high-sensitivity cardiac troponins tend to be higher than those in matched controls who do not have COPD, albeit within normal limits.[71] During exacerbations, high-sensitivity measurements show circulating cardiac troponin concentrations higher than the upper limit of normal in most cases, particularly in patients with known ischaemic heart disease.[6,9,10]

Although patients with clinically apparent acute cardiac disease have been excluded from previous investigations of raised cardiac troponin concentrations during COPD exacerbations,[6,7,9,10] the nature of cardiac injury in this setting was not assessed beyond basic clinical examination, electrocardiography, and chest radiographs—all of which have poor sensitivity for characterisation of cardiac disease in this setting. Thus, what troponin release during an exacerbation of COPD represents at a pathophysiological level remains unclear. Some evidence shows that the mortality associated with increased troponin concentrations in patients with COPD exacerbations might be linked to tachycardia.[10] Underlying left ventricular hypertrophy is also common in patients with COPD and could contribute to troponin increases in this setting.[72] Cardiac dysfunction during COPD exacerbations could also be caused by acute pulmonary hypertension and right ventricular dysfunction (raised troponin concentrations also occur in pulmonary hypertension caused by pulmonary embolism and predict adverse outcomes).[73]

Cardiac strain or stretch

B-type natriuretic peptides (BNPs) are secreted from ventricular cardiomyocytes in response to cardiac wall stretch as a result of either volume or pressure overload under sympathetic drive.[74] BNPs downregulate the sympathetic nervous system and the renin–angiotensin–aldosterone system, enable natriuresis, decrease peripheral vascular resistance, increase smooth-muscle relaxation, stimulate myocardial relaxation, and inhibit cardiac remodelling.[74] Assays for detection of physiologically active BNP and the metabolically inactive cleavage by-product, amino-terminal pro-BNP (NT-proBNP), are valuable in the diagnosis of heart failure and correlate with impaired left ventricular function detected by echocardiography.[74] However, mild-to-moderate increases also occur in situations other than clinical heart failure: BNP concentrations rise with age, and can be increased in renal impairment, hyperdynamic states including sepsis, and pulmonary hypertension.[74] Raised BNP concentrations are also noted in patients after acute myocardial infarction without symptoms of heart failure, when they are associated with an adverse short-term outlook.[75] High concentrations of BNPs predict an increased risk of cardiovascular events and death in asymptomatic people without heart failure, even after adjustment for other cardiovascular risk factors.[76] Serum BNP and NT-proBNP concentrations are often raised during exacerbations of COPD (table 2) and predict poor short-term and long-term prognosis.[18,19,35,44]

Taken together, evidence shows that cardiovascular diseases are common in stable COPD and that exacerbations of COPD are associated with an increased risk of both overt and subclinical acute cardiac dysfunction, both of which are associated with increased mortality. After acute exacerbations of COPD, the short-term (30 day), and, to some extent, long-term mortality of patients with high concentrations of BNPs and cardiac troponins are much higher than are those of patients with normal BNP and cardiac troponin concentrations, even after adjustment for exacerbation severity.[35,44] Furthermore, NT-proBNP and cardiac troponins are better indicators of short-term prognosis in COPD than are widely used clinical prognostic instruments, such as the confusion, urea, respiratory rate, blood pressure, and age older than 65 years (CURB-65) and elevated blood urea nitrogen, altered mental status, pulse greater than 109 beats per minute, and age older than 65 years (BAP-65) scores.[35] The dyspnoea, eosinopenia, consolidation, acidaemia, and atrial fibrillation (DECAF) score, which includes a cardiac parameter (ie, atrial fibrillation), might be more accurate than CURB-65 or BAP-65.[50]

Cardiac biomarkers could help to phenotype exacerbations of COPD to improve stratification of prognosis. They could also help to identify the cause of the exacerbation, but not enough is known about the mechanisms of cardiac dysfunction in COPD exacerbations to provide definitive guidelines for diagnosis and management.

	Study design	Study population (n)	Biomarkers	Key findings
Abroug et al, 2006[11]	Cross-sectional	Patients admitted to intensive-care unit (148)	NT-proBNP, troponin T	High NT-proBNP and troponin T concentrations were significantly associated with left ventricular dysfunction (p<0·0001)
Baillard et al, 2003[55]	Prospective cohort	Patients admitted to intensive-care unit (71)	Troponin I	High troponin I concentrations (>0·5 μg/L) were noted in 18% of population and associated with increased risk of in-hospital mortality (OR 6·52 [95% CI 1·23–34·47])
Brekke et al, 2008[33]	Retrospective cohort	Patients admitted to hospital (396)	Troponin I	High troponin I concentrations (≥0·04 μg/L) were associated with increased risk of all-cause mortality (HR 1·64 [95% CI 1·15–2·34])
Brekke et al, 2009[56]	Cross-sectional	Patients admitted to hospital (441)	Troponin T	High troponin T concentrations (>0·04 μg/L) were noted in 27% of population; independent determinants of increased concentrations were high neutrophil count, creatinine, heart rate, cardiac infarction injury score, and low haemoglobin concentrations
Campo et al, 2015[57]	Prospective cohort	Patients admitted to hospital (694)	Troponin T	High troponin T concentrations were noted in 70% of patients and associated with increased risk of cardiac mortality and non-fatal myocardial infarction (composite HR 1·73 [95% CI 1·2–2·7])
Chang et al, 2011[35]	Prospective cohort	Patients admitted to hospital (250)	NT-proBNP, troponin T	High NT-proBNP (>1864 ng/L; OR 9·0 [95% CI 3·1–26·2]) and troponin T (>0·03 μg/L; 6·3 [2·4–16·5]) concentrations were associated with increased risk of 30 day mortality
Fruchter et al, 2009[37]	Retrospective cohort	Patients admitted to hospital (182)	Troponin I	High troponin I concentrations (>0·03 μg/L) were noted in 59% of population and associated with increased risk of 3 year mortality (HR 1·32 [95% CI 1·08–2·25])
Gale et al, 2011[58]	Prospective cohort	Patients admitted to hospital (140)	NT-proBNP	The highest quartile NT-proBNP concentrations (>298 ng/L) were associated with increased risk of 1 year mortality (RR 3·02, p=0·001)
Gariani et al, 2011[15]	Cross-sectional	Patients admitted to hospital (57)	BNP	Increased BNP (>100 ng/L) in 81% of population, which had sensitivity of 92% and negative predictive value of 91% to detect left ventricular systolic failure and sensitivity of 93% and negative predictive value of 91% to detect left ventricular diastolic failure
Harvey et al, 2004[8]	Retrospective case series	Patients admitted to hospital (188)	Troponin I, troponin T	High troponins (>0·4 μg/L for troponin I or >0·03 μg/L for troponin T) in 25% of population, which were associated with longer hospital stays (5 days *vs* 3 days, p=0·001)
Hoiseth et al, 2011[59]	Prospective cohort	Patients admitted to hospital (99)	High-sensitivity troponin T	High troponin T concentrations (≥0·014 μg/L) were associated with increased long-term mortality (HRs 4·5 [95% CI 1·2–16·0] for troponin T 0·014–0·0399 μg/L and 8·9 [2·4–32·0] for troponin T ≥0·04 μg/L)
Hoiseth et al, 2012[10]	Cross-sectional	Patients admitted to hospital (99)	High-sensitivity troponin T	High troponin T concentrations were associated with older age, arterial hypertension, tachycardia, and increased serum creatinine (all p values <0·05)
Hoiseth et al, 2012[18]	Prospective cohort	Patients admitted to hospital (99)	NT-proBNP	Highest tertile NT-proBNP concentrations (≥909 ng/L) were noted in 74% of population and were associated with increased risk of long-term mortality (HR 3·2 [95% CI 1·3–8·1])
Hoiseth et al, 2014[60]	Prospective cohort	Patients admitted to hospital (83)	High-sensitivity troponin T, NT-proBNP	Stable increased troponin concentrations were associated with higher mortality (HR 2·4 [95% CI 1·1–5·3]), as were NT-proBNP concentrations >1181 ng/L (5·6 [1·8–17·0])
Inoue et al, 2009[61]	Prospective cohort	Patients with stable COPD admitted to hospital (60)	BNP	BNP concentration was higher during exacerbations of COPD than in stable disease (p=0·004) and correlated with left ventricular ejection fraction (r=–0·41, p=0·0197)
Kanat et al, 2007[62]	Randomised controlled trial	Patients with stable COPD admitted to hospital (45)	BNP	BNP concentrations were higher during exacerbations of COPD than in stable disease (p=0·0001) and significantly decreased from day 1 to day 10 of exacerbation (p<0·05); the decrease was more substantial with diuretic treatment and was independent of right ventricular dysfunction
Kelly et al, 2013[63]	Retrospective cohort	Patients admitted to hospital (252)	Troponin I	High troponin I concentrations (>0·04 μg/L, in 31 % of population) were associated with increased risk of in-hospital mortality (OR 8·3 [95% CI 1·58–43·70])
Marcun et al, 2012[44]	Prospective cohort	Patients admitted to hospital (127)	NT-proBNP, troponin T	High NT-proBNP concentrations (>95th percentile) were noted in 60% of population and predicted 6 month mortality (HR 4·2 [95% CI 1·07–14·01]), high discharge troponin T concentrations (>0·012 μg/L) were noted in 19% of population and predicted future admission to hospital (2·89 [1·13–7·36])
Martins et al, 2009[64]	Retrospective cohort	Patients admitted to hospital (173)	BNP, troponin I	High troponin I concentrations (>0·012 μg/L) in 70% of patients, which were associated with increased use of non-invasive ventilation and long-term mortality (p<0·01); high BNP concentrations (>100 ng/L) were noted in 76% of population
McAllister et al, 2012[7]	Case series	Patients admitted to hospital (242)	Troponin I, troponin T	High troponin concentrations (>99th percentile) in 10% of population
McCullough et al, 2003[65]	Cross-sectional	Emergency presentation (417*)	BNP	High BNP concentration (>100 ng/L, in 37 % of population) was the strongest predictor of heart failure (OR 12·1 [95% CI 5·4–27·0])
Medina et al, 2011[19]	Prospective cohort	Patients admitted to hospital (192*)	NT-proBNP	High NT-proBNP concentrations (>588 ng/L) were noted in 44% of population and predicted 1 year mortality (OR 3·9 [95% CI 1·46–10·47])
Nishimura et al, 2014[16]	Prospective cohort	Patients with stable COPD admitted to hospital (251)	BNP	BNP concentrations were higher during exacerbations of COPD than in stable disease, and higher during exacerbation than before and after exacerbation (all p values <0·001)
Ouanes et al, 2012[12]	Cross-sectional	Patients admitted to intensive-care unit (120)	NT-proBNP	Left ventricular dysfunction was noted in 48% of patients; high NT-proBNP concentrations were associated with left ventricular dysfunction (p<0·0001)
Patel et al, 2013[13]	Prospective cohort	Patients with COPD exacerbations in the community (98)	NT-proBNP, troponin T	NT-proBNP and troponin T concentrations were higher during the exacerbation than during stable disease, higher in patients with known ischaemic heart disease, and persistently increased more than 5 weeks after exacerbation (all p values <0·01)

(Table 2 continues on next page)

	Study design	Study population (n)	Biomarkers	Key findings
(Continued from previous page)				
Pavasini et al, 2015[6]	Systematic review and meta-analysis	Patients admitted to hospital (2062)	High-sensitivity troponin T, troponin I, troponin T	High troponin concentrations (high troponin T in 17–74% of the population and high troponin I in 18–70%) were associated with increased risk of all-cause mortality (OR 1·69 [95% CI 1·25–2·29]), mortality within 6 months (3·22 [1·31–7·91]), and mortality after more than 6 months (1·38 [1·02–1·86])
Sanchez-Marteles et al, 2009[66]	Case series	Patients admitted to hospital (99)	NT-proBNP	NT-proBNP concentrations were higher in patients older than 65 years and in patients with atrial fibrillation (p values <0·01)
Sanchez-Marteles et al, 2010[67]	Prospective cohort	Patients admitted to hospital (192)	NT-proBNP	High NT-proBNP concentrations (>500 ng/L) were noted in 53% of population and associated with increased risk of mortality at 6 months (OR 11·0 [95% CI 1·39–86·99)
Soyseth et al, 2013[9]	Cross-sectional	Patients with stable COPD admitted to hospital (174)	High-sensitivity troponin T	Troponin T concentrations were four-times higher during exacerbations than during stable disease (relative change 4·26 [95% CI 3·02–6·00)
Stiell et al, 2014[51]	Prospective cohort	Emergency presentation (945)	NT-proBNP, troponin T, troponin I	High NT-proBNP (>5000 ng/L) concentrations in 11% of patients and raised troponins (>99th percentile) in 13%; no significant difference in NT-proBNP (p=0·5) and troponin (p=0·9) concentrations between patients with and without serious adverse events
Stolz et al, 2008[14]	Prospective cohort	Emergency department presentations and recovery (208)	BNP	BNP concentrations were higher during exacerbation than during recovery (p<0·001); increased BNP concentrations were associated with admission to the intensive-care unit (HR 1·13 [95% CI 1·03–1·24] for an increase of 100 ng/L), but not associated with in-hospital, 6 month, or 2 year mortality
Yang et al, 2010[68]	Randomised controlled trial	Patients admitted to intensive-care unit (56)	BNP	Invasive ventilation reduced BNP concentrations more efficaciously after 24 hours' treatment than did non-invasive ventilation (p<0·05)
Youssef et al, 2013[69]	Cross-sectional	Patients admitted to hospital (60)	Troponin I	High troponin I concentrations (≥0·01 µg/L) were noted in 70% of population and associated with severity of exacerbations, right ventricular dysfunction, weaning failure from mechanical ventilation, and increased risk of in-hospital mortality (all p values <0·05)

COPD=chronic obstructive pulmonary disease. BNP=B-type natriuretic peptide. NT-proBNP=amino-terminal pro B-type natriuretic peptide. OR=odds ratio. RR=risk ratio. HR=hazard ratio. *Included patients with chronic asthma.

***Table 2*: Studies of cardiac biomarkers in exacerbations of COPD**

Possible mechanisms of cardiac dysfunction

Several mechanisms could plausibly be implicated in provoking cardiac distress during COPD exacerbation (figure 1). Respiratory infections increase the risk of vascular events and are the most common precipitant of exacerbation.[77] In a large prospective cohort of 20 101 exacerbations of COPD resulting in hospital admission (in which antibiotic prescription was a criterion to define exacerbation), myocardial infarction and stroke risk within the early period after admission were more than double the baseline risk.[78] Cardiac troponin and BNP concentrations are also increased in community-acquired pneumonia, suggesting an increased risk of acute cardiac dysfunction during acute respiratory infections.[79]

Hypoxaemia and tachycardia associated with a COPD exacerbation can lead to adverse cardiac effects, especially in patients with pre-existing coronary disease or left ventricular dysfunction. Infective COPD exacerbations also provoke acute increases in arterial stiffness (as assessed by aortic pulse wave velocity),[13] which then increases left ventricular afterload.

COPD is associated with systemic inflammation, which is increased during acute exacerbations. Plasma fibrinogen concentrations are associated with risk of COPD exacerbations and adverse outcomes.[80] Platelet activation is present in stable COPD and increases during exacerbations.[81] Concentrations of other pro-atherothrombotic biomarkers, such as interleukins 6 and 8 and tumour necrosis factor α, and prothrombin fragments are also raised during exacerbations. These findings suggest that exacerbations of COPD lead to systemic inflammation, hypercoagulability, increased platelet activation, and oxidative stress. These factors can cause endothelial dysfunction and precipitate atherosclerotic plaque rupture and thrombosis.[82]

Emphysema in stable patients is associated with reduced left ventricular filling and diastolic dysfunction on echocardiography.[83] Cardiac MRI studies show reduced biventricular filling and blood volumes in severe and even mild emphysema, which are thought to be secondary to lung hyperinflation raising intrathoracic pressures and impeding venous return.[84] High intrathoracic pressures generated by dynamic hyperinflation in acute exacerbations of COPD would be expected to further impede venous return.

β_2 agonists are part of standard treatment for COPD exacerbations, but have been associated with adverse cardiovascular effects.[85] In comorbid cardiorespiratory disease, increasing doses of β_2 agonists have been associated with an increase in admissions to hospital associated with heart failure and increased all-cause mortality.[86] Thus high doses of β_2 agonists given during acute severe COPD exacerbations could plausibly contribute to cardiac stress. β-agonist-induced cardiac

toxic effects in the setting of hypoxia were thought to be a possible cause of asthma deaths;[87] patients with COPD have a greater risk than do those with asthma because they are generally older, more hypoxaemic, and are more likely to have pre-existing cardiac comorbidities. Although β_2 agonists are thought to be safe at standard doses in stable COPD, the safety of the very high doses that are often used in COPD exacerbations has not been established in clinical trials. It is noteworthy that high-dose β_2-agonist therapy has been linked to cardiovascular mortality in COPD exacerbations[88] and that COPD exacerbations and overuse of β_2 agonists are increasingly recognised as a cause of stress cardiomyopathy.[89,90]

COPD exacerbations are associated with acute increases in pulmonary artery pressure,[91] and cardiac biomarker derangement might be a result of acute right heart strain. Acute right heart strain can also be associated with left ventricular dysfunction: raised pulmonary pressures in patients with stable COPD are associated with left ventricular diastolic dysfunction on echocardiograms,[92] and poor right heart function is usually associated with impaired left heart function in patients with COPD.[93]

COPD is associated with persistent autonomic dysfunction that is amplified during acute exacerbations. The physiological mechanism is not entirely understood, but includes blunted sensory and stretch receptor responses, arterial chemoreceptor upregulation due to hypoxaemia and hypercapnia, arterial and cardiac baroreceptor changes as a result of large fluctuations of intrathoracic pressure, neurohormonal activation secondary to systemic inflammation and the effect of exogenous β sympathomimetics. Taken together, these physiological processes result in increased sympathetic tone, loss of parasympathetic tone, reduced autonomic reflexes, and altered baroreceptor sensitivity, all of which are associated with adverse cardiac events.[94]

Determining how all these different mechanisms contribute to cardiac dysfunction in COPD exacerbations is a key challenge for research.

Recognition of cardiac dysfunction

Diagnosis of cardiac disease in COPD is difficult (figure 2). Electrocardiographic abnormalities are common in COPD exacerbations but under-recognised in clinical practice.[4,7] Additionally, recognition of an acute coronary syndrome is challenging because the traditional complex of chest pain, electrocardiographic changes, and increased troponin concentrations might be unreliable during an exacerbation of COPD. Many patients have electrocardiographic changes in the absence of acute cardiac injury,[7] chest discomfort associated with COPD exacerbation can be difficult to distinguish from cardiac pain, and troponins are frequently increased without other evidence of myocardial infarction.[6–8,10]

Assessment of the cardiothoracic ratio and interstitial oedema by chest radiography is obscured in patients with emphysema.[95] Transthoracic echocardiography is the most frequently used technique to assess cardiac failure. It is non-invasive and does not expose patients to radiation, but is associated with interobserver variability, necessitates assumptions about cardiac morphology and—pertinent to patients with COPD—works poorly in patients with emphysema because of impairment of the acoustic window.[12,16] Cardiac MRI is currently thought to be the gold standard for assessment of cardiac function (particularly the right ventricle).[96] However, the cost, duration, and claustrophobic nature of an MRI scanner are impractical for patients with an exacerbation of COPD.

Hence, as a result of the limitations of available techniques, the relative contributions of acute coronary disease and left ventricular or right ventricular pathological changes to the biomarker derangements and associated mortality noted in COPD exacerbations are difficult to distinguish. Dynamic cardiac CT is an emerging technique that can be used to assess biventricular function, pulmonary artery anatomy, coronary artery calcification, and pulmonary structure, and might inform future research and clinical

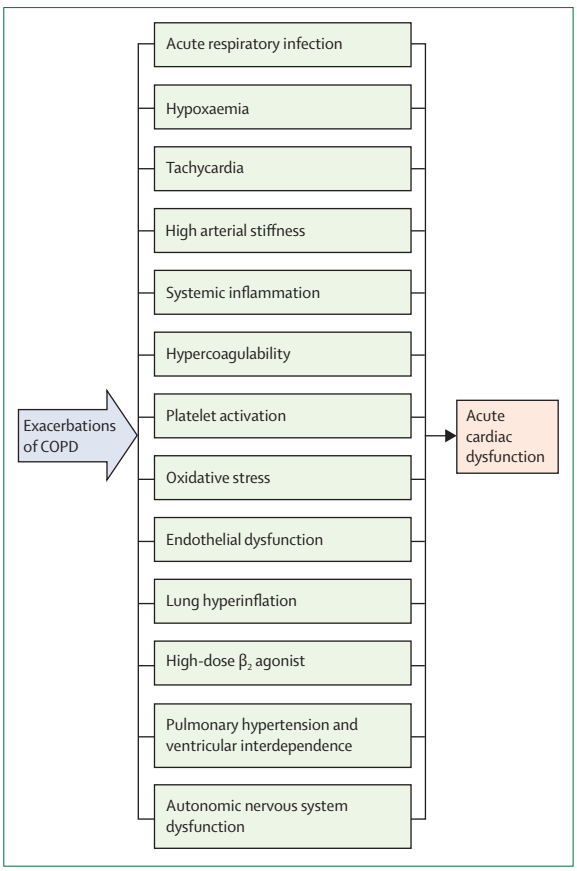

***Figure 1*: Potential factors contributing to acute cardiac dysfunction in exacerbations of COPD**
COPD=chronic obstructive pulmonary disease.

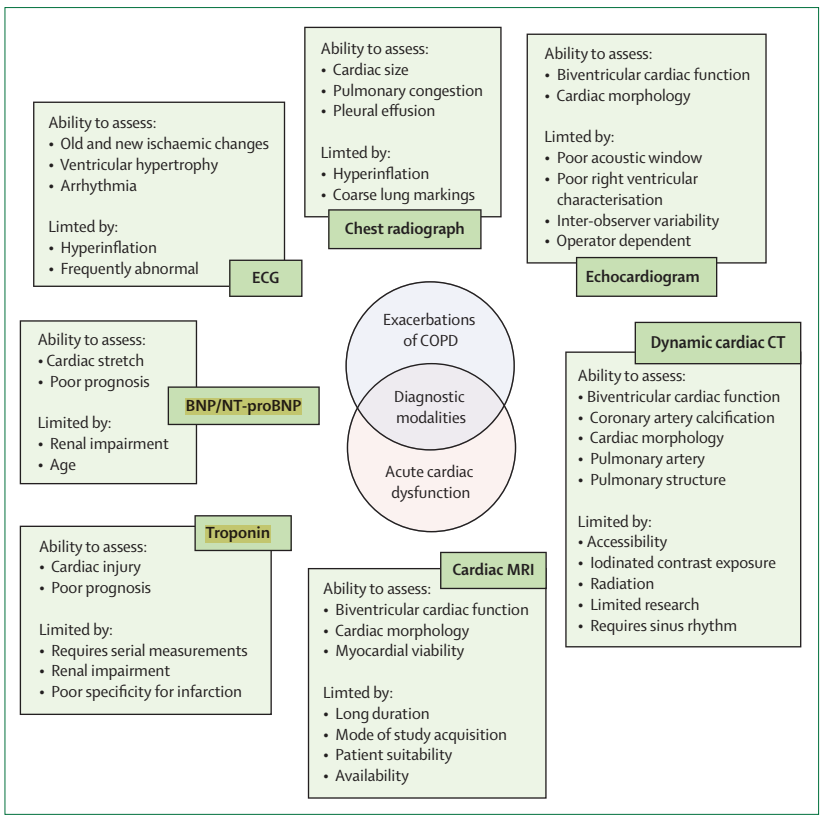

***Figure 2*: Advantages and limitations of diagnostic modalities of acute cardiac dysfunction in exacerbations of COPD**

COPD=chronic obstructive pulmonary disease. BNP=B-type natriuretic peptide. NT-proBNP=amino-terminal pro B-type natriuretic peptide. ECG=electrocardiography.

assessment of cardiac dysfunction in patients with COPD.

Treating cardiac disease in COPD exacerbations

Almost no evidence from clinical trials is available as a basis for management of cardiovascular disease during COPD exacerbations. In view of the prevalence and adverse consequences, cardiac involvement is an important topic for future research. Few existing COPD treatments reduce mortality from exacerbations and treatment of cardiovascular comorbidities could possibly have a greater effect on overall mortality than do specific respiratory treatments.

A particularly urgent question is whether cardioselective β blockers should routinely be used in patients with COPD. β blockers are an important component of the management of both ischaemic heart disease and heart failure, but have often been avoided in patients with airways disease for fear of inducing bronchospasm. Patients with COPD were excluded from the major randomised controlled trials[97] that showed the substantial mortality benefit associated with β blockers in heart failure. Short-term clinical trials suggest that patients with stable COPD can tolerate cardioselective β blockers,[98,99] but no long-term clinical trial evidence of the benefits and harms is available.

Despite the absence of evidence, there are good reasons to suspect that β blockers might have cardiovascular benefits in exacerbations of COPD. Patients with COPD often have high resting heart rates and sympathetic dominance of cardiac autonomic modulation,[100] which will be accentuated during exacerbations. In apparently healthy populations and those with known cardiac disease, resting heart rate is an independent risk factor for all-cause mortality.[101] The results of observational studies have shown that cardioselective β blockers are associated with lower mortality in stable COPD.[102] β blockers have also been associated with reduced exacerbation rates.[103] Furthermore, retrospective observational studies suggest that mortality is lower in patients who are taking β blockers at the time of an exacerbation than in those who are not,[36] but no prospective controlled trials have been done. Many considerations would have to be taken into account in an appropriate study. Use of a highly cardioselective β blocker in patients who depend on β_2-agonist bronchodilators seems logical. Identification of the target population at high cardiovascular risk could be based on predictive risk-scoring algorithms,[104] simple clinical markers such as tachycardia, serum cardiac biomarkers, or imaging (eg, coronary artery calcium scoring), depending on the balance between cost, accessibility, and precision.

Other perhaps less controversial options for treating cardiac disease in COPD exacerbations also need to be investigated. Ivabradine lowers the heart rate by specifically blocking the sinoatrial node, and could be an alternative to β blockers for patients in sinus rhythm.[105] Thrombocytosis has been associated with increased mortality from COPD exacerbations and patients taking antiplatelet drugs at the time of an exacerbation had lower 1 year mortality in an observational study.[39] Although in a 2014 randomised controlled trial, statins did not prevent COPD exacerbations,[106] the study was not designed or powered to assess cardiac outcomes and patients at high cardiovascular risk were excluded. Results of retrospective studies[107,108] suggest that mortality might be lower in patients with COPD who are taking statins than in those who are not. The results of observational studies[107,108] also suggest that angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers could reduce mortality in stable COPD and during exacerbations of disease, but these drugs have also not been assessed in clinical trials.

Many cardiac therapies have proven efficacy for primary indications in selected groups of patients. However, patients with COPD tend to be excluded from clinical trials of cardiac treatments (most notably trials of β blockers[109–111]). Although patients with COPD have a high risk of cardiac events and deaths, they might also

Search strategy and selection criteria

We searched PubMed with the terms "chronic obstructive pulmonary disease" or "COPD", "exacerbation", "cardiac failure" or "heart failure", "myocardial infarction", "troponin", and "BNP" or "NT-proBNP" for original research and reviews published in any language on or before Sept 1, 2015. We did not do a systematic review, and used the most relevant results. Further studies were identified from the reference lists of reviewed papers. For foreign language studies, translations were used.

be prone to increased adverse effects from cardiac treatments and the balance of risks and benefits of these treatments, even in stable disease, remains unclear. Future studies of cardiovascular treatments should include patients with COPD to determine whether both stable patients and those with disease exacerbations would benefit from cardiac treatment. However, we identified no ongoing clinical trials of cardiac treatment during COPD exacerbations on ClinicalTrials.gov or the Australian New Zealand Clinical Trials Registry when we used the search terms "chronic obstructive pulmonary disease" or "COPD", "cardiac treatment", "beta-blocker", and "statin". A feasibility study of β blockers in COPD exacerbations (ACTRN12614001095651) has been done and a randomised controlled trial of metoprolol for prevention of exacerbation (NCT02587351) has not yet commenced recruitment.

Conclusions

Accumulating evidence suggests that cardiac dysfunction during exacerbations of COPD is common and portends poor prognosis. The emphasis for treatment has been placed on optimisation of therapies for COPD itself—scant attention has been paid to the management of cardiovascular complications. However, convincing evidence suggests that a pulmonary exacerbation is often associated with cardiac exacerbations, but this co-occurrence is often not suspected and can be difficult to detect clinically with the current approach to assessment of patients with COPD exacerbations.

Few respiratory treatments substantially affect mortality from COPD exacerbations. Identification of cardiac dysfunction during exacerbations represents an opportunity to treat the primary, non-respiratory cause of mortality in COPD. Treating the heart could also have a greater effect on outcomes than treatment solely directed at the airways. Although there is tantalising evidence that active management of cardiac disease with β blockers, statins, and antiplatelet drugs could be beneficial, no randomised controlled trials have been done and none seem to be underway. There is an urgent need to understand cardiac dysfunction in COPD exacerbations and establish whether cardiac treatments improve outcomes.

Contributors

MIM and ES are the first authors. MIM, ES, CLC, PGB, and RJH conceived and designed the review, and contributed to data acquisition and critical analysis of published work. MIM and ES wrote the first draft. All authors contributed to critical revision of the report for important intellectual content and approved the final version to be published.

Declaration of interests

RJH has received lecture fees from Novartis and Glaxo Wellcome, lecture and advisory board fees from AstraZeneca, and non-financial support (ie, workshop attendance) from Boehringer, all of which were unrelated to this work . All other authors declare no competing interests.

References

1 Mullerova H, Agusti A, Erqou S, Mapel DW. Cardiovascular comorbidity in COPD: systematic literature review. *Chest* 2013; **144:** 1163–78.

2 Patel AR, Donaldson GC, Mackay AJ, Wedzicha JA, Hurst JR. The impact of ischemic heart disease on symptoms, health status, and exacerbations in patients with COPD. *Chest* 2012; **141:** 851–57.

3 Wang CS, FitzGerald JM, Schulzer M, Mak E, Ayas NT. Does this dyspneic patient in the emergency department have congestive heart failure? *JAMA* 2005; **294:** 1944–56.

4 Brekke PH, Omland T, Smith P, Soyseth V. Underdiagnosis of myocardial infarction in COPD—cardiac infarction injury score (CIIS) in patients hospitalised for COPD exacerbation. *Respir Med* 2008; **102:** 1243–47.

5 Connors AF Jr, Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *Am J Respir Crit Care Med* 1996; **154:** 959–67.

6 Pavasini R, d'Ascenzo F, Campo G, et al. Cardiac troponin elevation predicts all-cause mortality in patients with acute exacerbation of chronic obstructive pulmonary disease: systematic review and meta-analysis. *Int J Cardiol* 2015; **191:** 187–93.

7 McAllister DA, Maclay JD, Mills NL, et al. Diagnosis of myocardial infarction following hospitalisation for exacerbation of COPD. *Eur Respir J* 2012; **39:** 1097–103.

8 Harvey MG, Hancox RJ. Elevation of cardiac troponins in exacerbation of chronic obstructive pulmonary disease. *Emerg Med Australas* 2004; **16:** 212–15.

9 Soyseth V, Bhatnagar R, Holmedahl NH, et al. Acute exacerbation of COPD is associated with fourfold elevation of cardiac troponin T. *Heart* 2013; **99:** 122–26.

10 Hoiseth AD, Omland T, Hagve TA, Brekke PH, Soyseth V. Determinants of high-sensitivity cardiac troponin T during acute exacerbation of chronic obstructive pulmonary disease: a prospective cohort study. *BMC Pulm Med* 2012; **12:** 22.

11 Abroug F, Ouanes-Besbes L, Nciri N, et al. Association of left-heart dysfunction with severe exacerbation of chronic obstructive pulmonary disease: diagnostic performance of cardiac biomarkers. *Am J Respir Crit Care Med* 2006; **174:** 990–96.

12 Ouanes I, Jalloul F, Ayed S, et al. N-terminal proB-type natriuretic peptide levels aid the diagnosis of left ventricular dysfunction in patients with severe acute exacerbations of chronic obstructive pulmonary disease and renal dysfunction. *Respirology* 2012; **17:** 660–66.

13 Patel AR, Kowlessar BS, Donaldson GC, et al. Cardiovascular risk, myocardial injury, and exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; **188:** 1091–99.

14 Stolz D, Breidthardt T, Christ-Crain M, et al. Use of B-type natriuretic peptide in the risk stratification of acute exacerbations of COPD. *Chest* 2008; **133:** 1088–94.

15 Gariani K, Delabays A, Perneger TV, Agoritsas T. Use of brain natriuretic peptide to detect previously unknown left ventricular dysfunction in patients with acute exacerbation of chronic obstructive pulmonary disease. *Swiss Med Weekly* 2011; **141:** w13298.

16 Nishimura K, Nishimura T, Onishi K, Oga T, Hasegawa Y, Jones PW. Changes in plasma levels of B-type natriuretic peptide with acute exacerbations of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2014; **9:** 155–62.

17 Escande W, Duva Pentiah A, Coisne A, et al. Left ventricular myocardial performance index predicts poor outcome during COPD exacerbation. *Int J Cardiol* 2014; **173:** 575–79.

18 Hoiseth AD, Omland T, Hagve TA, Brekke PH, Soyseth V. NT-proBNP independently predicts long term mortality after acute exacerbation of COPD—a prospective cohort study. *Respir Res* 2012; **13:** 97.

19 Medina AM, Marteles MS, Saiz EB, et al. Prognostic utility of NT-proBNP in acute exacerbations of chronic pulmonary diseases. *Eur J Intern Med* 2011; **22:** 167–71.

20 Macchia A, Monte S, Romero M, D'Ettorre A, Tognoni G. The prognostic influence of chronic obstructive pulmonary disease in patients hospitalised for chronic heart failure. *Eur J Heart Fail* 2007; **9:** 942–48.

21 Stefan MS, Bannuru RR, Lessard D, Gore JM, Lindenauer PK, Goldberg RJ. The impact of COPD on management and outcomes of patients hospitalized with acute myocardial infarction: a 10-year retrospective observational study. *Chest* 2012; **141:** 1441–48.

22 Soriano JB, Rigo F, Guerrero D, et al. High prevalence of undiagnosed airflow limitation in patients with cardiovascular disease. *Chest* 2010; **137:** 333–40.

23 Lange P, Nyboe J, Jensen G, Schnohr P, Appleyard M. Ventilatory function impairment and risk of cardiovascular death and of fatal or non-fatal myocardial infarction. *Eur Respir J* 1991; **4:** 1080–87.

24 Kannel WB, Hubert H, Lew EA. Vital capacity as a predictor of cardiovascular disease: the Framingham study. *Am Heart J* 1983; **105:** 311–15.

25 Mannino DM, Doherty DE, Sonia Buist A. Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the atherosclerosis risk in communities (ARIC) study. *Respir Med* 2006; **100:** 115–22.

26 McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA, Committee TCE. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. *Thorax* 2007; **62:** 411–15.

27 Macchia A, Rodriguez Moncalvo JJ, Kleinert M, et al. Unrecognised ventricular dysfunction in COPD. *Eur Respir J* 2012; **39:** 51–58.

28 Boudestein LC, Rutten FH, Cramer MJ, Lammers JW, Hoes AW. The impact of concurrent heart failure on prognosis in patients with chronic obstructive pulmonary disease. *Eur J Heart Fail* 2009; **11:** 1182–88.

29 Curkendall SM, DeLuise C, Jones JK, et al. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. *Ann Epidemiol* 2006; **16:** 63–70.

30 Agabiti N, Belleudi V, Davoli M, et al. Profiling hospital performance to monitor the quality of care: the case of COPD. *Eur Respir J* 2010; **35:** 1031–38.

31 Almagro P, Calbo E, Ochoa de Echaguen A, et al. Mortality after hospitalization for COPD. *Chest* 2002; **121:** 1441–48.

32 Almagro P, Cabrera FJ, Diez-Manglano J, et al. Comorbidome and short-term prognosis in hospitalised COPD patients: the ESMI study. *Eur Respir J* 2015; **46:** 850–53.

33 Brekke PH, Omland T, Holmedal SH, Smith P, Soyseth V. Troponin T elevation and long-term mortality after chronic obstructive pulmonary disease exacerbation. *Eur Respir J* 2008; **31:** 563–70.

34 Bustamante-Fermosel A, De Miguel-Yanes JM, Duffort-Falco M, Munoz J. Mortality-related factors after hospitalization for acute exacerbation of chronic obstructive pulmonary disease: the burden of clinical features. *Am J Emerg Med* 2007; **25:** 515–22.

35 Chang CL, Robinson SC, Mills GD, et al. Biochemical markers of cardiac dysfunction predict mortality in acute exacerbations of COPD. *Thorax* 2011; **66:** 764–68.

36 Dransfield MT, Rowe SM, Johnson JE, Bailey WC, Gerald LB. Use of beta blockers and the risk of death in hospitalised patients with acute exacerbations of COPD. *Thorax* 2008; **63:** 301–05.

37 Fruchter O, Yigla M. Cardiac troponin-I predicts long-term mortality in chronic obstructive pulmonary disease. *COPD* 2009; **6:** 155–61.

38 Fuso L, Incalzi RA, Pistelli R, et al. Predicting mortality of patients hospitalized for acutely exacerbated chronic obstructive pulmonary disease. *Am J Med* 1995; **98:** 272–77.

39 Harrison MT, Short P, Williamson PA, Singanayagam A, Chalmers JD, Schembri S. Thrombocytosis is associated with increased short and long term mortality after exacerbation of chronic obstructive pulmonary disease: a role for antiplatelet therapy? *Thorax* 2014; **69:** 609–15.

40 Hasegawa W, Yamauchi Y, Yasunaga H, et al. Factors affecting mortality following emergency admission for chronic obstructive pulmonary disease. *BMC Pulm Med* 2014; **14:** 151.

41 Antonelli Incalzi R, Fuso L, De Rosa M, et al. Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. *Eur Respir J* 1997; **10:** 2794–800.

42 Lainscak M, von Haehling S, Doehner W, et al. Body mass index and prognosis in patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease. *J Cachexia Sarcopenia Muscle* 2011; **2:** 81–86.

43 Lindenauer PK, Grosso LM, Wang C, et al. Development, validation, and results of a risk-standardized measure of hospital 30-day mortality for patients with exacerbation of chronic obstructive pulmonary disease. *J Hosp Med* 2013; **8:** 428–35.

44 Marcun R, Sustic A, Brguljan PM, et al. Cardiac biomarkers predict outcome after hospitalisation for an acute exacerbation of chronic obstructive pulmonary disease. *Int J Cardiol* 2012; **161:** 156–59.

45 McGhan R, Radcliff T, Fish R, Sutherland ER, Welsh C, Make B. Predictors of rehospitalization and death after a severe exacerbation of COPD. *Chest* 2007; **132:** 1748–55.

46 Raurich JM, Perez J, Ibanez J, Roig S, Batle S. In-hospital and 2-year survival of patients treated with mechanical ventilation for acute exacerbation of COPD. *Archivos de Bronconeumologia* 2004; **40:** 295–300.

47 Roberts CM, Stone RA, Lowe D, Pursey NA, Buckingham RJ. Co-morbidities and 90-day outcomes in hospitalized COPD exacerbations. *COPD* 2011; **8:** 354–61.

48 Slenter RH, Sprooten RT, Kotz D, Wesseling G, Wouters EF, Rohde GG. Predictors of 1-year mortality at hospital admission for acute exacerbations of chronic obstructive pulmonary disease. *Respiration* 2013; **85:** 15–26.

49 Soyseth V, Brekke PH, Smith P, Omland T. Statin use is associated with reduced mortality in COPD. *Eur Respir J* 2007; **29:** 279–83.

50 Steer J, Gibson J, Bourke SC. The DECAF score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. *Thorax* 2012; **67:** 970–76.

51 Stiell IG, Clement CM, Aaron SD, et al. Clinical characteristics associated with adverse events in patients with exacerbation of chronic obstructive pulmonary disease: a prospective cohort study. *CMAJ* 2014; **186:** E193–204.

52 Tabak YP, Sun X, Johannes RS, Hyde L, Shorr AF, Lindenauer PK. Development and validation of a mortality risk-adjustment model for patients hospitalized for exacerbations of chronic obstructive pulmonary disease. *Med Care* 2013; **51:** 597–605.

53 Terzano C, Conti V, Di Stefano F, et al. Comorbidity, hospitalization, and mortality in COPD: results from a longitudinal study. *Lung* 2010; **188:** 321–29.

54 Wildman MJ, Sanderson C, Groves J, et al. Predicting mortality for patients with exacerbations of COPD and Asthma in the COPD and asthma outcome study (CAOS). *QJM* 2009; **102:** 389–99.

55 Baillard C, Boussarsar M, Fosse JP, et al. Cardiac troponin I in patients with severe exacerbation of chronic obstructive pulmonary disease. *Intensive Care Med* 2003; **29:** 584–89.

56 Brekke PH, Omland T, Holmedal SH, Smith P, Soyseth V. Determinants of cardiac troponin T elevation in COPD exacerbation—a cross-sectional study. *BMC Pulm Med* 2009; **9:** 35.

57 Campo G, Pavasini R, Malagu M, et al. Relationship between troponin elevation, cardiovascular history and adverse events in patients with acute exacerbation of COPD. *COPD* 2015; **12:** 560–67.

58 Gale CP, White JE, Hunter A, et al. Predicting mortality and hospital admission in patients with COPD: significance of NT pro-BNP, clinical and echocardiographic assessment. *J Cardiovasc Med (Hagerstown)* 2011; **12:** 613–18.

59 Hoiseth AD, Neukamm A, Karlsson BD, Omland T, Brekke PH, Soyseth V. Elevated high-sensitivity cardiac troponin T is associated with increased mortality after acute exacerbation of chronic obstructive pulmonary disease. *Thorax* 2011; **66:** 775–81.

60 Hoiseth AD, Neukamm A, Hagve TA, Omland T, Brekke PH, Soyseth V. The clinical value of serial measurement of high-sensitivity cardiac troponin T in acute exacerbations of chronic obstructive pulmonary disease. *Open Heart* 2014; **1:** e000001.

61 Inoue Y, Kawayama T, Iwanaga T, Aizawa H. High plasma brain natriuretic peptide levels in stable COPD without pulmonary hypertension or cor pulmonale. *Intern Med* 2009; **48:** 503–12.

62 Kanat F, Vatansev H, Teke T. Diuretics, plasma brain natriuretic peptide and chronic obstructive pulmonary disease. *Neth J Med* 2007; **65:** 296–300.

63 Kelly AM, Klim S. Is elevated troponin associated with in-hospital mortality in emergency department patients admitted with chronic obstructive pulmonary disease? *Eur J Emerg Med* 2013; **20:** 54–57.

64 Martins CS, Rodrigues MJ, Miranda VP, Nunes JP. Prognostic value of cardiac troponin I in patients with COPD acute exacerbation. *Neth J Med* 2009; **67:** 341–49.

65 McCullough PA, Hollander JE, Nowak RM, 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.

66 Sanchez-Marteles M, Cecilio-Irazola A, Vano-Sanchis D, Nuviala-Mateo R, Serrano-Martinez S, Perez-Calvo JJ. NT-proBNP in chronic obstructive pulmonary disease patients. *An Sist Sanit Navar* 2009; **32:** 235–41 (in Spanish).

67 Sanchez-Marteles M, Molina Medina A, Bermejo Saiz E, Ruiz Laiglesia F, Nieto Rodriguez JA, Perez-Calvo JI. Prognostic value of NT-proBNP in chronic pulmonary disease exacerbation. *Medicina Clinica* 2010; **135:**441–46 (in Spanish).

68 Yang HH, Zhou Y. Effect of invasive and non-invasive positive pressure ventilation on plasma brain natriuretic peptide in patients with chronic obstructive pulmonary disease and severe respiratory failure. *Nan fang yi ke da xue xue bao* 2010; **30:** 2377–79 (in Chinese).

69 Youssef ARI, Hassan ASA, El-Ghamry R, Ahmed AE. Serum troponin-I as a prognostic marker in acute exacerbated chronic obstructive pulmonary disease patients. *Egypt J Chest Dis Tuberculosis* 2013; **62:** 549–55.

70 Alcalai R, Planer D, Culhaoglu A, Osman A, Pollak A, Lotan C. Acute coronary syndrome *vs* nonspecific troponin elevation: clinical predictors and survival analysis. *Arch Intern Med* 2007; **167:** 276–81.

71 Neukamm AM, Hoiseth AD, Hagve TA, Soyseth V, Omland T. High-sensitivity cardiac troponin T levels are increased in stable COPD. *Heart* 2013; **99:** 382–87.

72 Anderson WJ, Lipworth BJ, Rekhraj S, Struthers AD, George J. Left ventricular hypertrophy in COPD without hypoxemia: the elephant in the room? *Chest* 2013; **143:** 91–97.

73 Giannitsis E, Muller-Bardorff M, Kurowski V, et al. Independent prognostic value of cardiac troponin T in patients with confirmed pulmonary embolism. *Circulation* 2000; **102:** 211–17.

74 Daniels LB, Maisel AS. Natriuretic peptides. *J Am Coll Cardiol* 2007; **50:** 2357–68.

75 Pesaro AE, Katz M, Caixeta A, et al. Prognostic value of serial brain natriuretic peptide measurements in patients with acute myocardial infarction. *Cardiol* 2015; **131:** 116–21.

76 Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004; **350:** 655–63.

77 Clayton TC, Thompson M, Meade TW. Recent respiratory infection and risk of cardiovascular disease: case-control study through a general practice database. *Eur Heart J* 2008; **29:** 96–103.

78 Donaldson GC, Hurst JR, Smith CJ, Hubbard RB, Wedzicha JA. Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010; **137:** 1091–97.

79 Chang CL, Mills GD, Karalus NC, et al. Biomarkers of cardiac dysfunction and mortality from community-acquired pneumonia in adults. *PloS One* 2013; **8:** e62612.

80 Duvoix A, Dickens J, Haq I, et al. Blood fibrinogen as a biomarker of chronic obstructive pulmonary disease. *Thorax* 2013; **68:** 670–76.

81 Maclay JD, McAllister DA, Johnston S, et al. Increased platelet activation in patients with stable and acute exacerbation of COPD. *Thorax* 2011; **66:** 769–74.

82 Malerba M, Clini E, Malagola M, Avanzi GC. Platelet activation as a novel mechanism of atherothrombotic risk in chronic obstructive pulmonary disease. *Expert Rev Hematol* 2013; **6:** 475–83.

83 Boussuges A, Pinet C, Molenat F, 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:** 670–75.

84 Jorgensen K, Muller MF, Nel J, Upton RN, Houltz E, Ricksten SE. Reduced intrathoracic blood volume and left and right ventricular dimensions in patients with severe emphysema: an MRI study. *Chest* 2007; **131:** 1050–57.

85 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.

86 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:** 1964–69.

87 McDevitt DG, Shanks RG, Swanton JG. Further observations on the cardiotoxicity of isoprenaline during hypoxia. *Br J Pharmacol* 1974; **50:** 335–44.

88 Buajordet I, Ebbesen J, Erikssen J, Brors O, Hilberg T. Fatal adverse drug events: the paradox of drug treatment. *J Intern Med* 2001; **250:** 327–41.

89 Rajwani A, Adam Z, Hall JA. Bronchogenic stress cardiomyopathy: a case series. *Cardiol* 2015; **130:** 106–11.

90 Madias JE. Bronchogenic stress cardiomyopathy, a subset of Takotsubo syndrome. *Cardiol* 2015; **131:** 160.

91 Wells JM, Washko GR, Han MK, et al. Pulmonary arterial enlargement and acute exacerbations of COPD. *N Engl J Med* 2012; **367:** 913–21.

92 Acikel M, Kose N, Aribas A, et al. The effect of pulmonary hypertension on left ventricular diastolic function in chronic obstructive lung disease: a tissue doppler imaging and right cardiac catheterization study. *Clin Cardiol* 2010; **33:** E13–18.

93 MacNee W, Xue QF, Hannan WJ, Flenley DC, Adie CJ, Muir AL. Assessment by radionuclide angiography of right and left ventricular function in chronic bronchitis and emphysema. *Thorax* 1983; **38:** 494–500.

94 Van Gestel AJ, Steier J. Autonomic dysfunction in patients with chronic obstructive pulmonary disease (COPD). *J Thoracic Dis* 2010; **2:** 215–22.

95 Hublitz UF, Shapiro JH. Atypical pulmonary patterns of congestive failure in chronic lung disease. The influence of pre-existing disease on the appearance and distribution of pulmonary edema. *Radiology* 1969; **93:** 995–1006.

96 Kumar A, Patton DJ, Friedrich MG. The emerging clinical role of cardiovascular magnetic resonance imaging. *Can J Cardiol* 2010; **26:** 313–22.

97 Domanski MJ, Krause-Steinrauf H, Massie BM, et al. A comparative analysis of the results from 4 trials of beta-blocker therapy for heart failure: BEST, CIBIS-II, MERIT-HF, and COPERNICUS. *J Card Fail* 2003; **9:** 354–63.

98 Hawkins NM, MacDonald MR, Petrie MC, et al. Bisoprolol in patients with heart failure and moderate to severe chronic obstructive pulmonary disease: a randomized controlled trial. *Eur J Heart Fail* 2009; **11:** 684–90.

99 Chang CL, Mills GD, McLachlan JD, Karalus NC, Hancox RJ. Cardio-selective and non-selective beta-blockers in chronic obstructive pulmonary disease: effects on bronchodilator response and exercise. *Intern Med J* 2010; **40:** 193–200.

100 Chhabra SK, Gupta M, Ramaswamy S, Dash DJ, Bansal V, Deepak KK. Cardiac sympathetic dominance and systemic inflammation in COPD. *COPD* 2015; **12:** 552–59.

101 Jensen MT, Suadicani P, Hein HO, Gyntelberg F. Elevated resting heart rate, physical fitness and all-cause mortality: a 16-year follow-up in the Copenhagen male study. *Heart* 2013; **99:** 882–87.

102 Du Q, Sun Y, Ding N, Lu L, Chen Y. Beta-blockers reduced the risk of mortality and exacerbation in patients with COPD: a meta-analysis of observational studies. *PloS One* 2014; **9:** e113048.

103 Bhatt SP, Wells JM, Kinney GL, et al. Beta-blockers are associated with a reduction in COPD exacerbations. *Thorax* 2015; published online Aug 17. DOI: 10.1136/thoraxjnl-2015-207251.

104 Cazzola M, Calzetta L, Matera MG, Muscoli S, Rogliani P, Romeo F. Chronic obstructive pulmonary disease and coronary disease: COPDCoRi, a simple and effective algorithm for predicting the risk of coronary artery disease in COPD patients. *Respir Med* 2015; **109:** 1019–25.

105 Riccioni G. Ivabradine: the hope for a good treatment of ischemic heart disease. *Curr Med Chem* 2013; **20:** 1817–23.

106 Criner GJ, Connett JE, Aaron SD, et al. Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. *New Engl J Med* 2014; **370:** 2201–10.

107 Mortensen EM, Copeland LA, Pugh MJ, et al. Impact of statins and ACE inhibitors on mortality after COPD exacerbations. *Respir Res* 2009; **10:** 45.

108 Mancini GB, Etminan M, Zhang B, Levesque LE, FitzGerald JM, Brophy JM. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. *J Am Coll Cardiol* 2006; **47:** 2554–60.

109 MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). *Lancet* 1999: **353:** 2001–07.

110 CIBIS-II investigators and committees. The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. *Lancet* 1999; **353:** 9–13.

111 ISIS-1 (First International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. *Lancet* 1986; **328:** 57–66.