Biochemical markers of cardiac dysfunction predict mortality in acute exacerbations of COPD

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ABSTRACT

Background Retrospective studies suggest that plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiac troponin T are often elevated in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) and are associated with increased mortality. These cardiac biomarkers were investigated in an unselected cohort of patients admitted to hospital with exacerbations of COPD.

Methods Consecutive patients with physician-diagnosed COPD exacerbation but without clinical evidence of acute cardiac disease admitted to a public hospital over a 1 year period were studied prospectively. NT-proBNP and troponin T were measured on admission. The primary end point was all-cause mortality at 30 days.

Results Elevated NT-proBNP (>220 pmol/l) was present in 65/244 patients (27.5%) and significantly predicted 30-day mortality (OR 9.0, 95% CI 3.1 to 26.2, p<0.001). Elevated troponin T (>0.03 μg/l) was found in 40/241 patients (16.6%) and also predicted 30-day mortality (OR 6.3, 95% CI 2.4 to 16.5, p<0.001). These associations persisted after adjusting for other clinical and laboratory predictors of mortality (arterial CO_2 pressure ($Paco_2$), body mass index and CURB65 score). NT-proBNP and troponin T levels appeared to have additive associations with mortality: 30-day mortality among patients with abnormalities of both NT-proBNP and troponin T was 15-fold higher than among patients with normal values.

Conclusion Elevated levels of NT-proBNP and troponin T are strong predictors of early mortality among patients admitted to hospital with acute exacerbations of COPD independently of other known prognostic indicators. The pathophysiological basis for this is unknown, but indicates that cardiac involvement in exacerbations of COPD may be an important determinant of prognosis.

Key messages

What is the key question?
► Does subclinical cardiac involvement influence mortality in acute exacerbation of COPD?

What is the bottom line?
► Elevated levels of NT-proBNP and troponin T strongly predict 30-day mortality in patients with acute exacerbations of COPD independently of other markers of severity and prognosis.

Why read on?
► The findings from this prospective study of cardiac biomarkers in COPD exacerbation suggest that we may need to re-think the causes of death in these patients.

Brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are established markers of left ventricular dysfunction and are associated with increased mortality in acute and stable heart disease.[5][6] They are also increased with right ventricular overload and associated with a poor prognosis in pulmonary arterial hypertension and pulmonary thromboembolism.[7–9]

Cardiac troponins are specific markers of myocardial necrosis and commonly used to diagnose myocardial infarction.[10] Elevated troponin levels may also occur in pulmonary thromboembolism, congestive heart failure, tachyarrhythmias, myocarditis, pericarditis, sepsis and stroke.[11] Troponin elevations in these conditions probably reflect general myocardial injury rather than coronary arterial occlusion. We have retrospectively observed that cardiac troponins are frequently raised in COPD exacerbations and appear to be associated with the severity of the exacerbation.[12] There are few prospective data on the prognostic value of cardiac troponins in patients with exacerbations of COPD.

To investigate cardiac involvement in acute COPD exacerbations, we prospectively analysed the associations between NT-proBNP and troponin T levels and mortality in a prospective cohort of consecutive patients admitted to hospital with exacerbations of COPD.

INTRODUCTION

Cardiovascular disease is common in patients with chronic obstructive pulmonary disease (COPD) and is associated with poorer prognosis in COPD exacerbations.[1][2] The degree to which cardiac disease contributes to mortality during exacerbations of COPD is unknown, but accumulating evidence suggests that this may be substantial. Severe hypoxaemia, pulmonary hypertension and systemic inflammation due to exacerbations of COPD may impact on cardiac function, but the interplay of these factors and their cardiovascular effects in COPD is incompletely understood.[3][4]

MATERIALS AND METHODS

Detailed methods are given in the online supplement.

Consecutive patients admitted to Waikato Hospital with exacerbations of COPD over 1 year

were recruited. Patients were excluded if there was evidence of another acute respiratory illness (such as acute asthma or pneumonia) or if the main reason for hospitalisation was not COPD exacerbation. Patients diagnosed with coronary ischaemia were excluded. For patients admitted more than once during the study period, only the first admission was included in the analysis. Treatment was not influenced by participation in the study. Medical history and physiological variables were recorded on admission. These data were used to compile two prognostic scores: BAP65 and CURB65.[13] [14] NT-proBNP and troponin T were measured within 24 h of admission and were categorised as normal or elevated according to local reference values. The primary end point was 30-day mortality. Mortality between 30 days and 1 year was a secondary end point. Logistic regression was used to adjust associations between NT-proBNP, troponin T and mortality for potential confounders including age, lung function, arterial blood gases, CURB65 score, BAP65 score and body mass index (BMI). Only variables with univariate associations of $p \leq 0.05$ were included in the multiple logistic regression models. Mortality in patients with different cardiac marker status (normal; elevated NT-proBNP and normal troponin T; normal NT-proBNP and elevated troponin T; and both elevated NT-proBNP and troponin T) was compared using χ^2 tests.

RESULTS

Two hundred and fifty-one consecutive patients met the inclusion criteria, of whom 250 consented to participate (table 1). Survival information was available for 248 (99%) at 30 days and 227 (91%) at 1 year. Thirty-seven percent had very severe airway obstruction (forced expiratory volume in 1 s (FEV_1) <30% predicted), 44% had severe airway obstruction (FEV_1 30–50% predicted) and 19% had mild/moderate airway obstruction.[16] Lung function was not measured in seven patients due to inpatient death or inability to perform spirometry. Nine patients did not meet spirometric criteria for COPD.[16] Excluding these patients from the analysis made no difference to the findings. The 30-day and 1-year mortality were 8.5% (21/248) and 18.5% (42/227), respectively.

NT-proBNP levels were available for 244 (98%) patients. The median level was 66.5 pmol/l (range 2–3900). Sixty-five patients had elevated levels (>220 pmol/l). Elevated NT-proBNP predicted mortality at 30 days (table 2) but did not predict deaths between 30 days and 1 year of follow-up (p=0.27) (figure 1). Analysed as a continuous variable using logistic regression, the OR of 30-day mortality associated with each SD increase of log-NT-proBNP was 2.6 (95% CI, 1.542 to 4.432, p<0.001).

Troponin T levels were available for 241 (97%) patients. Seventy-four percent were below the lower limit of detection at 0.01 μg/l. The troponin T level was elevated (>0.03 μg/l) in 40 (16.6%) patients. Elevated troponin T levels predicted mortality at 30 days (OR 6.3, p<0.001) (table 2) but did not predict deaths between 30 days and 1 year of follow-up (p=0.63) (figure 1).

NT-proBNP and troponin T levels were correlated (Spearman rho=0.46, p<0.001). In logistic regression analyses using both biomarkers, a raised NT-proBNP predicted 30-day mortality (OR 6.71, p=0.001), but raised troponin T levels were of borderline significance (OR 2.74, p=0.066). Patients with both raised troponin T and raised NT-proBNP had the highest risk of 30-day mortality (figure 2).

In univariate analyses, pH, arterial CO_2 pressure ($PaCO_2$), BMI and CURB65 scores also predicted 30-day mortality, whereas lung function (FEV_1% predicted, FEV_1/forced vital capacity (FVC)), PaO_2, BAP65 score and age did not. $PaCO_2$ and pH were

highly correlated (Spearman rho=0.76) and did not predict mortality independently of each other. In multivariate analysis, a high NT-proBNP remained a significant predictor of 30-day mortality independently of $PaCO_2$ (or pH), BMI and CURB65 score (table 2). A high troponin T was also a significant predictor of 30-day mortality independently of $PaCO_2$, BMI and CURB65 score, but failed to achieve statistical significance if NT-proBNP was included in the analysis (table 2). A past history of cardiovascular disease was associated with high NT-proBNP levels (χ^2=9.1, p=0.003) but did not predict 30-day mortality. Troponin T levels were not associated with a past history of cardiac disease (χ^2=0.11, p=0.74).

DISCUSSION

Elevated NT-proBNP and troponin T were strongly associated with increased early mortality in this unselected cohort of patients admitted to hospital with exacerbations of COPD. These biomarkers appeared to have an additive association with risk: patients with abnormalities of both NT-proBNP and troponin T had a 15-fold higher mortality at 30 days than patients with normal values for both markers (figure 2). The pathophysiological processes underlying the derangements in these biomarkers and how they relate to increased mortality in exacerbations of COPD are unknown. However, patients without abnormalities of NT-proBNP or troponin T had a low mortality, and this suggests that cardiac involvement may be an important determinant of prognosis in COPD exacerbations.

Table 1 Cohort characteristics

Sex, n (%)	
Male	112 (45)
Female	138 (55)
Ethnicity (%)	
European	197 (79)
Maori	43 (17)
Other	10 (4)
Age, mean in years (SD)	71.7 (10.6)
European	73 (10.3)
Maori	67 (9.9)
Smoking status (%)	
Current smoker	83 (33)
Ex-smoker	159 (63)
Never	8 (3.2)
Lung function—mean (SD)	
FEV_1 (litres)	0.81 (0.34)
FEV_1 (% predicted)*	35 (15)
FEV_1/FVC (%)	44 (14)
BMI—mean (SD)	25.3 kg/m² (7.0)
Co-morbidities, n (%)	
Renal insufficiency	22 (8.8)
Malignancy	23 (9.2)
Cardiovascular disease	75 (30.1)
Cerebral vascular disease	28 (11.2)
Liver disease	2 (0.8)
None of the above	141 (56.6)
Treatment, n (%)	
Systemic corticosteroids	245 (98)
Antimicrobial therapy	241 (96)
Bronchodilating agents	250 (100)
Non-invasive ventilation	24 (9.6)
Ventilation via endotracheal tube	2 (1)
Intensive/high dependency care admission	15 (6.0)

*Predicted reference, European Respiratory Society recommended reference equations 1993.[15]

Table 2 Univariate and logistic regression analyses of risk factors for death at 30 days in patients hospitalised for acute exacerbation of chronic obstructive pulmonary disease

Variable	Univariate analysis			Multivariate logistic regression		
	OR	p Value	95% CI	OR	p Value	95% CI
Age, years	1.032	0.171	0.99 to 1.08			
BMI, kg/m^2	0.925	0.035	0.86 to 0.99	0.905	0.029	0.83 to 0.99
Lung function						
FEV_1, litres	0.504	0.392	0.11 to 2.42			
% predicted FEV_1, %	0.998	0.923	0.97 to 1.03			
FEV_1/FVC, %	1.0	0.998	0.96 to 1.04			
$PaCO_2$, mm Hg	1.049	<0.0001	1.03 to 1.07	1.041	0.002	1.02 to 1.07
PaO_2, mm Hg	0.996	0.683	0.98 to 1.02			
CRP, mg/l	1.05	0.949	0.99 to 1.07			
Clinical scores						
BAP65, increment by 1	1.665	0.065	0.97 to 2.86			
CURB65, increment by 1	2.171	<0.0001	1.42 to 3.32	1.684	0.075	0.95 to 2.98
Past medical history						
Cardiovascular disease	0.701	0.504	0.25 to 1.99			
Cerebral vascular disease	1.990	0.248	0.62 to 6.40			
Malignancy	0.466	0.467	0.06 to 3.64			
Biochemical markers of cardiac dysfunction						
NT-proBNP >220 pmol/l	9.034	<0.0001	3.11 to 26.25	7.455	0.004	1.92 to 28.90
				9.241*	0.001	2.58 to 33.05
Troponin T >0.03 μg/l	6.333	<0.0001	2.43 to 16.50	2.468	0.138	0.75 to 8.15
				5.115†	0.003	1.73 to 15.15

Multivariate logistic regression was performed only on risk factors significant in univariate analyses (BMI, pco₂, CURB65 score, high NT-proBNP and high troponin T). Results for elevated NT-proBNP and troponin T are presented before and after adjustments for each other. ORs refer to the change in odds of mortality at 30 days associated with an increase in the predictor variables by one of the respective units.
*Analyses include all other variables in the multivariate model except elevated troponin T.
†Analyses include all other variables in the multivariate model except elevated NT-proBNP.
BMI, body mass index; CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Although NT-proBNP and troponin T predicted mortality independently of other prognostic indicators, it remains unclear whether cardiac involvement is a direct cause of mortality or whether these biomarkers just reflect the severity of the exacerbation. In severe COPD, hypoxia and pulmonary vaso-constriction can cause pulmonary hypertension and right ventricular dysfunction.[17] Tachycardia, ventilation—perfusion mismatch and respiratory muscle fatigue also contribute to cardiac stress, which may be exacerbated by an increased oxygen cost of breathing and increased left ventricular afterload from dynamic hyperinflation. Perhaps surprisingly, oxygen tension on arterial blood gas measurement was not associated with either elevated cardiac biomarkers or mortality. However, we cannot rule out the possibility that hypoxaemia earlier in the exacerbation may have contributed to these: many patients are treated with supplemental oxygen prior to hospitalisation and the arterial oxygenation measurements made on admission could have been influenced by this.

Alternatively, cardiac involvement may be due to a parallel process: many patients with COPD have co-existing coronary artery disease and systemic inflammation is associated with endothelial dysfunction and a procoagulant state.[1 18] Hence, coronary ischaemia may be more likely to occur in the setting of an acute COPD exacerbation.[19] However, none of the patients in our cohort had a clinical diagnosis of acute coronary syndrome. Moreover, there was only a weak correlation between C-reactive protein levels and NT-proBNP (Spearman rho=0.16, p=0.01) and no correlation between C-reactive protein and troponin T (rho=0.07, p=0.3), indicating that the severity of the systemic inflammatory response was not a major determinant of cardiac involvement.

Elevated levels of NT-proBNP and troponin T did not predict deaths between 30 days and 1 year. This suggests that these

biomarkers reflect the acute pathology of a severe exacerbation rather than general frailty. In keeping with this, NT-proBNP and troponin T predicted 30-day mortality independently of markers
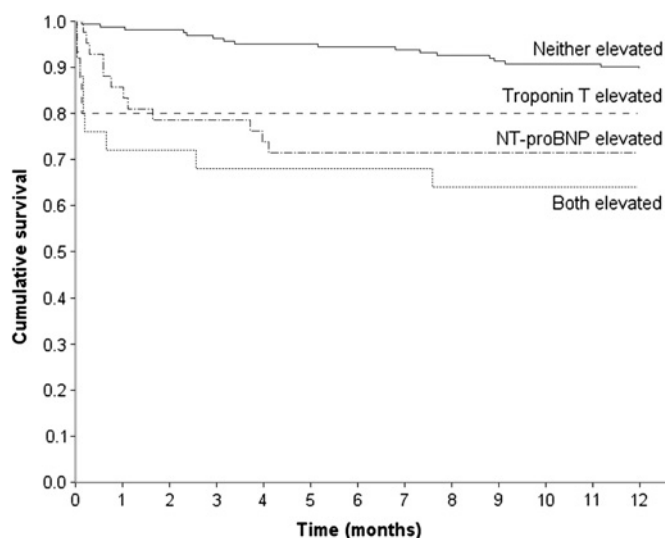
Figure 1 Kaplan—Meier survival curve for patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) stratified according to cardiac biomarker status. Survival was worse in patients with both biomarkers elevated compared with patients with normal biomarkers (log-rank test, p<0.0001). Survivals in patients with elevated N-terminal pro-brain natriuretic protein (NT-proBNP) and cardiac troponin T alone are also significantly different from those in patients with neither biomarkers elevated (log-rank test, p<0.001 and p=0.004 respectively).

Figure 2 Thirty-day mortality after exacerbation of chronic obstructive pulmonary disease (COPD) according to markers of cardiac dysfunction status (%). Thirty-day mortality was significantly lower in patients who had normal N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin T levels (three deaths among 163 patients) compared with patients who had elevated troponin T alone (2/14, p=0.05), elevated NT-proBNP alone (7/42), p=0.0007) and both elevated troponin T and NT-proBNP (7/25, p<0.0001). Mortality between groups was compared using χ^2 test.
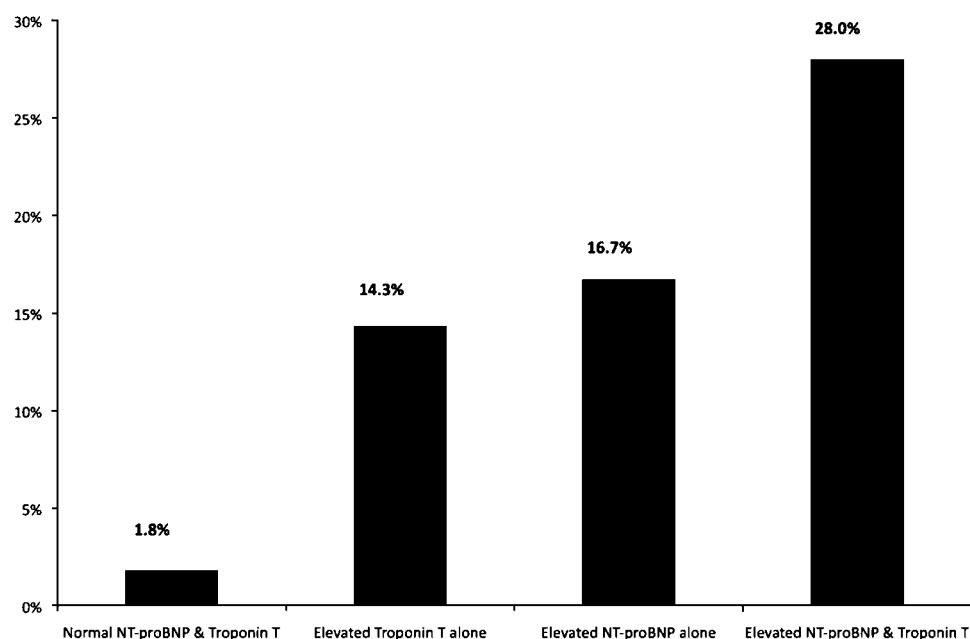
of chronic disease severity and reduced physiological reserve (lung function, BMI and age) as well as clinical and laboratory indicators of the severity of the presentation ($PaCO_2$ and severity score).

It is unclear whether elevated levels of NT-proBNP were primarily due to right or left ventricular dysfunction. Previous research has found that BNP and NT-proBNP may be elevated in patients with right ventricular pressure overload due to pulmonary arterial hypertension, pulmonary thromboembolism, undifferentiated chronic lung disease and respiratory failure where they are also associated with a poor prognosis.[8 9 20 21] On the other hand, high levels of NT-proBNP have been associated with left ventricular dysfunction in severe COPD exacerbations requiring ventilatory support.[22] Stolz et al previously found that raised BNP during COPD exacerbations predicted the need for intensive care, but levels of BNP observed in that study were lower than values typically found in patients with left ventricular failure.[23] This is confirmed in our study in which elevated levels of NT-proBNP were generally much lower than levels found in left ventricular failure.[24]

Elevated troponins have been associated with adverse outcomes in retrospective studies of COPD exacerbations.[12 25—27] These retrospective observations are limited by the potential for measurement bias—patients may be more likely to have troponins measured if they have a history of cardiovascular disease or evidence of cardiac dysfunction. Only one other study has prospectively assessed the prognostic significance of cardiac troponins in exacerbations of COPD, but this was limited to critically ill patients admitted to intensive care.[28] It also found that elevated troponins predicted increased mortality.

The strengths of the present study include the prospective design and the recruitment of all but one patient hospitalised for exacerbation of COPD during the study period. To our knowledge, this is the first time that markers of ventricular overload (NT-proBNP) and myocardial necrosis (troponin T) have been jointly assessed in an unselected cohort of patients with acute exacerbations of COPD. None of the patients was clinically diagnosed or treated for acute coronary syndromes or acute cardiac failure. Although this was a non-intervention study, the

clinicians were not blinded to the results of the cardiac biomarkers and it is possible that patient treatment was influenced by these. However, since treatment would be expected to improve patient outcomes, any treatments would be more likely to cause an underestimation of the difference in mortality. Although we were unable to confirm COPD in a small number of patients, either because they did not have spirometry or because their spirometry did not meet strict GOLD (Global Initiative for Obstructive Lung Disease) criteria, excluding these patients from the analysis made no material difference to the findings.[29]

Should patients with elevated NT-proBNP or troponin T but no clinical evidence of acute cardiac dysfunction be treated differently from patients with normal values? Increasing evidence suggests they should. A recent autopsy series of 43 consecutive patients who died within 24 h of hospitalisation for acute exacerbation of COPD found that cardiac failure was the leading cause of death.[30] There is also observational evidence to support cardioprotective treatment with β-blockers in stable COPD.[31 32] Patients receiving β-blockers appear to have a lower risk of COPD exacerbations[33] and a lower mortality from exacerbations.[33 34] Other cardioprotective treatments including statins and angiotensin-converting enzyme (ACE) inhibitors may also be beneficial in patients with COPD.[35 36] Our data suggest that cardiac involvement occurs frequently in acute exacerbations and that its presence predicts a poor prognosis. It is possible that active treatment of cardiac disease would improve outcomes, but we are not aware of any trials of acute cardiac treatment in this setting. Taken together, these findings point to an urgent need to investigate further the role of cardiac dysfunction and its treatment in COPD exacerbations.

In summary, elevated levels of NT-proBNP and troponin T predict early mortality in patients with acute exacerbations of COPD independently of other known prognostic factors. The pathophysiological basis of this is unknown, but the findings indicate the importance of cardiac dysfunction in these patients. NT-proBNP and troponin T may help clinicians to assess prognosis in exacerbations of COPD, but further research is needed to determine if they should influence treatment.

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