Cardiovascular Risk, Myocardial Injury, and Exacerbations of Chronic Obstructive Pulmonary Disease

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Rationale: Patients with chronic obstructive pulmonary disease (COPD) have elevated cardiovascular risk, and myocardial injury is common during severe exacerbations. Little is known about the prevalence, magnitude, and underlying mechanisms of cardiovascular risk in community-treated exacerbations.

Objectives: To investigate how COPD exacerbations and exacerbation frequency impact cardiovascular risk and myocardial injury, and whether this is related to airway infection and inflammation.

Methods: We prospectively measured arterial stiffness (aortic pulse wave velocity [aPWV]) and cardiac biomarkers in 98 patients with stable COPD. Fifty-five patients had paired stable and exacerbation assessments, repeated at Days 3, 7, 14, and 35 during recovery. Airway infection was identified using polymerase chain reaction.

Measurements and Main Results: COPD exacerbation frequency was related to stable-state arterial stiffness (rho = 0.209; $P = 0.040$). Frequent exacerbators had greater aPWV than infrequent exacerbators (mean ± SD aPWV, 11.4 ± 2.1 vs. 10.3 ± 2.0 ms^{-1}; $P = 0.025$). Arterial stiffness rose by an average of 1.2 ms^{-1} (11.1%) from stable state to exacerbation (n = 55) and fell slowly during recovery. In those with airway infection at exacerbation (n = 24) this rise was greater (1.4 ± 1.6 vs. 0.7 ± 1.3 ms^{-1}; $P = 0.048$); prolonged; and related to sputum IL-6 (rho = 0.753; $P < 0.001$). Increases in cardiac biomarkers at exacerbation were higher in those with ischemic heart disease (n = 12) than those without (n = 43) (mean ± SD increase in troponin T, 0.011 ± 0.009 vs. 0.003 ± 0.006 μg/L, $P = 0.003$; N-terminal pro–brain natriuretic peptide, 38.1 ± 37.7 vs. 5.9 ± 12.3 pg/ml, $P < 0.001$).

Conclusions: Frequent COPD exacerbators have greater arterial stiffness than infrequent exacerbators. Arterial stiffness rises acutely during COPD exacerbations, particularly with airway infection. Increases in arterial stiffness are related to inflammation, and are slow to recover. Myocardial injury is common and clinically significant during COPD exacerbations, particularly in those with underlying ischemic heart disease.

Keywords: chronic obstructive pulmonary disease; exacerbation; arterial stiffness; troponin; brain natriuretic peptide

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Patients with chronic obstructive pulmonary disease (COPD) have elevated cardiovascular risk, and myocardial injury commonly occurs during severe exacerbations. Little is known about the prevalence, magnitude, and underlying mechanisms of cardiovascular risk in community-treated exacerbations.

What This Study Adds to the Field

Frequent COPD exacerbators have greater arterial stiffness than infrequent exacerbators. Arterial stiffness rises acutely during COPD exacerbations, particularly with airway infection. Increases in arterial stiffness are related to airway inflammation, and are slow to recover. Myocardial injury is common and clinically significant during COPD exacerbations, particularly in those with underlying ischemic heart disease.

Chronic obstructive pulmonary disease (COPD) is a common and disabling condition affecting hundreds of millions of people worldwide and the third leading cause of global mortality behind ischemic heart disease (IHD) and stroke (1). Comorbidities and exacerbations are recognized to contribute to the complexity of COPD (2) and mortality from the disease (3, 4).

Acute exacerbations of COPD are common and important events, usually related to airway infection and inflammation (5). A phenotype of patients suffering from more frequent exacerbations (frequent exacerbators) is seen across all grades of COPD severity (6). Frequent exacerbators also have a worse health-related quality of life (7) and accelerated lung function decline (8) than infrequent exacerbators.

Cardiovascular comorbidity in general and IHD in particular is prevalent and important in patients with COPD beyond shared risk factors, such as age and smoking (9). The presence of IHD in COPD negatively impacts health status, symptoms, exercise capacity, exacerbation recovery time (10), hospitalizations, and mortality (11).

Epidemiologic data demonstrate a high-risk time period for cardiovascular events after acute respiratory infections in the general population (12) and exacerbations in patients with COPD (13). Moreover, a higher frequency of COPD exacerbations was associated with increasing incidence of myocardial infarction (13). This epidemiologic concept is supported by evidence that cardiac biomarkers of myocardial injury and dysfunction are commonly raised in patients hospitalized with COPD exacerbations (14) and are independent predictors of mortality (15). The relevance of this to most community-treated events has not previously been studied.

There are likely to be multiple mechanisms underlying heightened cardiovascular risk during exacerbations including tachycardia,

a procoagulant state (16, 17), and increased inflammation (18). Arterial stiffness is a well-validated noninvasive measure of cardiovascular risk, and predictive of cardiovascular events in a number of disease states and healthy controls (19, 20). Arterial stiffness is higher in patients with COPD than age-, sex-, and smoking-matched control subjects and may be an important mechanism underlying the observed increase in cardiovascular risk (21).

We hypothesized that cardiovascular risk and subclinical myocardial injury (measured by arterial stiffness and blood cardiac biomarkers) would be raised in frequent exacerbator patients and increase during community-treated acute COPD exacerbations. Furthermore, we hypothesized that the magnitude of these changes may be related to airway infection and inflammation. This is important in targeting cardiovascular risk reduction strategies in stable COPD and at exacerbation.

Some of the results of these studies have previously been reported in abstract form (22–24).

METHODS

Study Subjects

We prospectively collected and analyzed data from patients enrolled in the London COPD Cohort. This observational cohort and the inclusion and exclusion criteria have been described in many previous publications (7, 8, 10).

Definitions of Clinical Status

The definition and identification of COPD exacerbations using daily symptom diary cards have been previously described (10) and is available in the online supplement.

We reviewed 98 patients at more than one sequential stable-state visit (stable defined as no exacerbation symptoms or therapy 4 wks before and 2 wks after the attendance), which occurred several months apart.

We assessed 55 patients in the stable state and acutely at exacerbation presentation and subsequently during recovery. Thirty of these patients were included in both analyses. Patients were asked to attend recovery monitoring visits at Days 3 (±1), 7 (±2), 14 (±2), and 35 (±3) after the initial exacerbation visit. Recurrent exacerbations occurring within this 5-week follow-up period were not included in this study, and recovery monitoring for the index exacerbation was halted in this instance.

We sampled patients if they presented within 7 days of exacerbation symptom onset and had not yet taken any systemic therapy, such as antibiotics or oral corticosteroids. We treated all 55 acute exacerbations in this study with oral antibiotics and/or systemic corticosteroids. None of the patients had symptoms suggestive of an acute coronary syndrome.

Clinical Assessment and Sampling

Prior to spirometry, arterial stiffness was assessed using Vicorder apparatus and software (Skidmore Medical Ltd, Gloucester, UK) to measure carotid-femoral aortic pulse wave velocity (aPWV), the gold standard noninvasive technique (25). Higher aPWV values indicate increased central arterial stiffness and increased cardiovascular risk. Detailed methods can be found in the online supplement.

Post-bronchodilator FEV_1 and FVC were measured as previously described (10). Resting peripheral blood pressure and heart rate were recorded at each visit using a calibrated automatic sphygmomanometer (Omron MX3 Plus; Omron Healthcare, Hoofddorp, the Netherlands). Pulse oximetry was also measured (Onyx 9500; Nonin Medical Inc, Minneapolis, MN).

Blood and Sputum Sampling and Processing

Serum C-reactive protein (CRP), N-terminal pro–brain natriuretic peptide (NT-proBNP), and troponin T were measured using a Modular Analytics E 170 Module (Roche, Burgess Hill, UK) with limits of detection of 1 mg/L, 2 pg/ml, and 0.003 μg/L, respectively. Plasma fibrinogen was analyzed using the Clauss method (IL ACL Top Coagulation Analyzer; Instrumentation Laboratories, Lexington, MA).

Spontaneously expectorated sputum was processed as soon as possible after collection to prevent RNA degradation. Processing methods can be found in the online supplement.

We performed multiplex bacterial polymerase chain reaction (PCR) as previously described for the most prevalent bacterial pathogens in stable and exacerbated COPD: *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* (26). The lower limit of detection for this technique was 1×10^4 colony-forming units per milliliter and this is therefore a sensitive test for clinically significant numbers of these specific bacteria.

We also performed reverse transcriptase PCR for human rhinovirus, the most prevalent virus at COPD exacerbation, as previously described (27). The sensitivity of this technique was also high with a lower limit of detection of 10.23 plaque-forming units per milliliter.

Sputum supernatant IL-6 and IL-8 were quantified using commercial sandwich ELISA kits (R&D Systems, Abingdon, England) with lower limits of detection of 0.7 and 7.5 pg/ml, respectively.

Determination of Exacerbation Frequency

Exacerbation frequency for each patient was calculated from diary card data as previously described (10) and outlined in the online supplement. Frequent exacerbators were defined as those with two or more symptom-defined exacerbations per year and infrequent exacerbators had less than two per year. We also identified subjects who had frequent healthcare use-defined exacerbations, which required prescription of antibiotics and/or systemic corticosteroids.

Statistical Analysis

Data were analyzed using STATA 8 software (StataCorp, College Station, TX) and IBM SPSS 19 (IBM Corporation, Armonk, NY). Details of the statistical tests used are reported in the online supplement.

Ethical Considerations

Research ethics approval was obtained from the Research Ethics Committee of the Royal Free Hampstead NHS Trust where this work was undertaken. All subjects provided written informed consent.

RESULTS

Clinical Characteristics of Study Population

The stable-state clinical characteristics, cardiovascular assessment, and biomarker assays from the patients with COPD for each analysis are reported in Table 1. The patients had moderate to severe airflow limitation and an extensive smoking history.

Cardiovascular Risk in Stable Patients with COPD

Arterial stiffness in the stable state was related to COPD exacerbation frequency ($r = 0.209$; $P = 0.040$) and, accordingly, frequent exacerbators had greater arterial stiffness than infrequent exacerbators (mean ± SD aPWV, 11.4 ± 2.1 [n = 26] vs. 10.3 ± 2.0 ms^{-1} [n = 72]; $P = 0.025$) (Figure 1). When exacerbations were defined by healthcare use alone, frequent exacerbators still had a higher arterial stiffness than infrequent exacerbators (mean ± SD aPWV, 11.8 ± 2.1 [n = 20] vs. 10.3 ± 2.0 ms^{-1} [n = 78]; $P = 0.005$). Peripheral mean arterial pressure was higher in frequent exacerbators (102.4 ± 6.6 [n = 72] vs. 98.2 ± 11.1 mm Hg [n = 26]; $P = 0.039$) with no difference in resting heart rate (79.3 ± 13.1 vs. 78.4 ± 12.6 beats per minute; $P = 0.119$). The higher arterial stiffness associated with being a frequent exacerbator was independent of age, sex, history of IHD, and mean arterial pressure ($\beta = 1.04$ [95% confidence interval (CI), 0.13–1.94]; $P = 0.026$).

In keeping with previously published data, therefore validating our results, aPWV correlated with increasing age ($r = 0.402$; $P < 0.001$) was higher in men than women (11.0 ± 2.2 [n = 60] vs. 10.0 ± 1.8 ms^{-1} [n = 38]; $P = 0.024$) and in those with IHD

TABLE 1. STABLE-STATE CLINICAL CHARACTERISTICS, CARDIOVASCULAR RISK, AND BIOMARKERS IN SUBJECTS WITH COPD

	98 Patients with COPD (*Stable*)	55 Patients with COPD (*Exacerbation Time Course*)
Mean (±SD) age, yr	72.1 (±8.9)	72.1 (±8.4)
Male	61%	58%
Ischemic heart disease	20%	22%
Current smoking	20%	20%
Long-term oxygen therapy	4%	0%
Median (IQR) smoking, pack-years	45 (25–79)	44 (21–74)
Mean (±SD) FEV_1, L	1.25 (±0.54)	1.14 (±0.41)
Mean (±SD) FEV_1, % predicted	52.0 (±18.9)	46.7 (±18.5)
Mean (±SD) FEV_1/FVC ratio	0.47 (±0.13)	0.46 (±0.14)
Median (IQR) exacerbation frequency, per yr	1.0 (0.5–2.0)	2.0 (1.0–3.6)
Mean (±SD) body mass index, kg/m^2	26.8 (±5.6)	27.1 (±5.5)
Mean (±SD) systolic blood pressure, mm Hg	137.0 (±21.8)	137.1 (±20.1)
Mean (±SD) diastolic blood pressure, mm Hg	79.9 (±10.0)	80.0 (10.9)
Mean (±SD) mean arterial pressure, mm Hg	99.0 (±14.1)	99.2 ± 11.0
Mean (±SD) heart rate, beats per minute	78.8 (±13.8)	76.0 (±12.9)
Mean (±SD) pulse oximetry, %	94.7 (±2.3)	94.7 (±2.2)
Mean (±SD) aortic pulse wave velocity, ms^{-1}	10.6 (±2.1)	10.1 (±1.7)
Mean (±SD) serum troponin T, μg/L	0.014 (±0.006)	0.012 (±0.006)
Median (IQR) serum N-terminal pro–brain natriuretic peptide, pg/ml*	12 (5–25)	12 (5–22)
Median (IQR) serum C-reactive protein, mg/L*	2.0 (1.0–6.0)	4.0 (2.0–8.5)
Mean (±SD) plasma fibrinogen, g/L	3.6 (±0.6)	3.8 (±0.6)
Median (IQR) sputum IL-6, pg/ml	477 (234–1,322)	791 (381–1,953)
Median (IQR) sputum IL-8, pg/ml	14,688 (4,748–27,871)	17,472 (8,657–33,269)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; IQR = interquartile range.

A total of 98 patients were assessed at more than one stable-state visit. Fifty-five patients were assessed in the stable state, at exacerbation, and during recovery. Thirty subjects were common to both groups.

* Serum N-terminal pro–brain natriuretic peptide and C-reactive protein were at or below the limit of detection in 2 and 12 of the 98 stable patients, respectively, and in 4 and 1 of the 55 exacerbating patients.

compared with those without (11.4 ± 2.7 [n = 20] vs. 10.4 ± 1.8 ms^{-1} [n = 78]; $P = 0.049$). Arterial stiffness was related to the severity of airflow limitation as assessed by FEV_1/FVC ratio ($r = -0.211$; $P = 0.038$), but not $FEV_{1\%}$ predicted ($r = -0.155$; $P = 0.131$).

Arterial stiffness in patients with stable COPD was related to serum troponin T (rho = 0.350; $P = 0.001$) but not NT-proBNP (rho = 0.161; $P = 0.146$). COPD exacerbation frequency did not relate to stable-state serum troponin T or NT-proBNP (rho = −0.039, $P = 0.717$ and rho = −0.110, $P = 0.324$, respectively).

In the 42 (43%) patients with COPD who produced a sputum sample in the stable state, aPWV was not significantly higher in those colonized with either typical airway bacteria or rhinovirus compared with those with no evidence for these pathogens (11.0 ± 3.2 [n = 12] vs. 10.3 ± 1.8 ms^{-1} [n = 30]; $P = 0.353$).

Arterial stiffness in stable COPD was related to serum CRP, in keeping with the existing literature (rho = 0.233; $P = 0.026$), but not to plasma fibrinogen (rho = 0.174; $P = 0.109$).

There was also no relationship between stable-state airway inflammation and arterial stiffness. Sputum IL-6 and IL-8 were not significantly related to aPWV (rho = 0.054, $P = 0.753$ and rho = 0.105, $P = 0.535$, respectively).

Arterial stiffness measurements in the stable state were reliable over time. Values remained relatively unchanged over several months with mean ± SD aPWV values of 10.6 ± 2.1, 10.4 ± 1.7, and 10.5 ± 1.9 ms^{-1} at the first, second (median [interquartile range] interval of 103 (91–175) d; n = 98), and third (interval of 91 (84–98) d; n = 27) visits, respectively. Across all visits, the coefficient of variation was 5.95%, with an intraclass correlation of 0.778 and an interitem correlation of 0.782.

Cardiovascular Risk during COPD Exacerbations

Time course of arterial stiffness during COPD exacerbations. Our data support the concept that exacerbations are associated with increased cardiovascular risk. Arterial stiffness was acutely elevated at COPD exacerbation presentation by 1.2 ms^{-1} (11.1%) compared with the paired stable-state level (mean ± SD aPWV, 11.3 ± 2.3 vs. 10.1 ± 1.7 ms^{-1}; $P < 0.001$) (Table 2, Figure 2). Other changes in relevant physiologic and biochemical parameters are reported in Table 2. In a multivariate analysis, the rise in arterial stiffness at exacerbation was independent of changes in mean arterial pressure, heart rate, and oxygen saturation as measured by pulse oximetry (β = 1.45 [95% CI, 0.41–2.45]; $P = 0.011$).

The mean ± SD time from the stable-state visit to exacerbation presentation visit was 90 ± 62 days. The time from exacerbation symptom onset to aPWV measurement was 3.6 ± 1.8 days. We detected trends between the magnitude of the change in aPWV and that in serum CRP and plasma fibrinogen (rho = 0.280, $P = 0.059$; $r = 0.311$, $P = 0.069$, respectively). All 55 acute

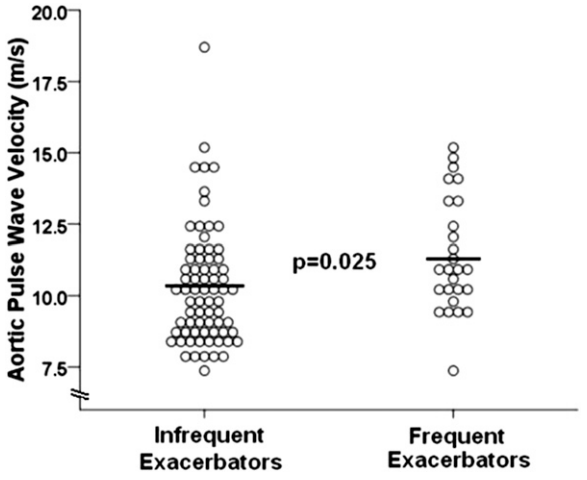

Figure 1. Frequent chronic obstructive pulmonary disease exacerbators (n = 72) had a higher stable-state arterial stiffness than infrequent exacerbators (n = 26) (mean ± SD aortic pulse wave velocity, 11.4 ± 2.1 vs. 10.3 ± 2.0 ms^{-1}; $P = 0.025$).

TABLE 2. CLINICAL CHARACTERISTICS AND BIOMARKERS OF 55 PATIENTS WITH COPD IN THE STABLE STATE AND AT EXACERBATION

	Stable State	Exacerbation	*P* Value
FEV_1, L, mean ± SD	1.14 ± 0.41	1.02 ± 0.39	0.145
FEV_1, % predicted, mean ± SD	46.7 ± 18.5	44.0 ± 0.13	0.160
FEV_1/FVC ratio, mean ± SD	0.46 ± 0.14	0.44 ± 0.13	0.371
Sp_{O_2}, %, mean ± SD	94.7 ± 2.2	93.9 ± 2.7	0.135
Systolic blood pressure, mm Hg, mean ± SD	137.1 ± 20.1	139.7 ± 16.6	0.592
Diastolic blood pressure, mm Hg, mean ± SD	80.0 ± 10.9	81.5 ± 11.6	0.604
Mean arterial pressure, mm Hg, mean ± SD	99.2 ± 11.0	100.1 ± 12.7	0.920
Aortic pulse wave velocity, ms^{-1}, mean ± SD	10.1 ± 1.7	11.3 ± 2.3	<0.001
Heart rate, beats per minute, mean ± SD	76.0 ± 12.9	84.0 ± 13.8	0.029
Plasma fibrinogen, g/L, mean ± SD	3.8 ± 0.6	4.2 ± 0.8	0.015
Serum C-reactive protein, mg/L, median (IQR)	4.0 (2.0–8.5)	14 (4.0–42.0)	<0.001

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; IQR = interquartile range; Sp_{O_2} = oxygen saturation as measured by pulse oximetry.

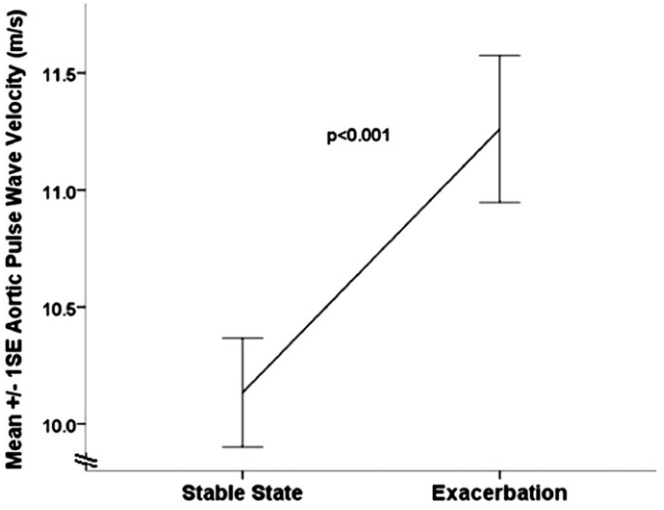

Figure 2. In 55 patients with chronic obstructive pulmonary disease, arterial stiffness increased acutely at exacerbation presentation compared with the paired stable state (mean ± SE aortic pulse wave velocity, 11.3 ± 0.4 vs. 10.1 ± 0.3 ms^{-1}; $P < 0.001$).

exacerbations studied were subsequently treated with oral antibiotics and/or systemic corticosteroids; 4 with antibiotics alone, 5 with corticosteroids alone, and 46 with both.

This increased arterial stiffness at exacerbation of COPD persisted for more than 2 months: during the subsequent 5 weeks, aPWV fell from its peak at exacerbation presentation by an average of 0.017 $ms^{-1}day^{-1}$ (95% CI, 0.001–0.033; $P = 0.040$) (Figure 3).

The increase in arterial stiffness at exacerbation of COPD was most pronounced in those patients with airway infection at exacerbation. Almost two-thirds of patients (36 [65%] of 55) produced a viable sputum sample at their exacerbation visit. Two-thirds of these exacerbation sputum producers (24 [67%] of 36) had either a typical bacterial pathogen or rhinovirus detected by PCR. Subjects with identifiable airway infection at exacerbation had a greater rise in arterial stiffness from the stable state to exacerbation than those with no infection or no sputum (1.4 ± 1.6 [n = 24] vs. 0.7 ± 1.3 ms^{-1} [n = 29]; $P = 0.048$) (Figure 4). Those with airway infection at exacerbation presentation also had elevated arterial stiffness that persisted for longer during the 5-week recovery period (Figure 4) (area under the curve [AUC], 38.2 ± 52.9 [n = 24] vs. 9.9 ± 42.9 ms^{-1} per 35 d [n = 29]; $P = 0.036$).

In addition to the presence of infection, arterial stiffness at exacerbation was also related to airway inflammation (aPWV and sputum IL-6, rho = 0.421; $P = 0.001$). This relationship seems to be driven by airway inflammation in those with airway infection (n = 19; rho = 0.753; $P < 0.001$) rather than those without infection or sputum (n = 13; rho = −0.110; $P = 0.721$).

Time course of cardiac biomarkers during COPD exacerbations. Further evidence of an acute rise and persistence in cardiovascular risk at exacerbation is provided by our analysis of cardiac biomarkers. Biomarkers of myocardial injury and dysfunction rose at COPD exacerbation from the stable state by a clinically significant margin (mean [± SD] troponin T 0.012 [± 0.011] vs. 0.017 [± 0.016] μg/L, $P < 0.001$; NT-proBNP 23.1 [± 39.2] vs. 36.0 [± 56.5] pg/ml, $P < 0.001$).

Increases in cardiac biomarkers from the stable state to exacerbation were significantly higher in those with known IHD (n = 12) compared with those without (n = 43) (mean [± SD] increase in troponin T, 0.011 [± 0.009] vs. 0.003 [± 0.006] μg/L, $P = 0.003$; NT-proBNP, 38.1 [± 37.7] vs. 5.9 [± 12.3] pg/ml, $P < 0.001$) (Figures 5A and 5B).

The increase in cardiac biomarkers persisted over the 5-week study period: serum troponin and NT-proBNP did not fall significantly during the initial 5 weeks postexacerbation (−0.0003 μg/L/day [95% CI, −0.0008 to 0.0004], $P = 0.431$; −0.096 pg/ml/day [95% CI, −0.631 to 0.438], $P = 0.723$).

Serum cardiac biomarker levels remained greater in subjects with COPD with known IHD (n = 12) than those without IHD (n = 43) during the 5-week recovery period (troponin T AUC, 0.368 ± 0.311 vs. 0.088 ± 0.174 μg/L per 35 d, $P < 0.001$; NT-proBNP AUC, 1,590 ± 2,620 vs. 279 ± 725 pg/ml per 35 d, $P = 0.005$) (Figures 5A and 5B).

Although providing complimentary assessments of cardiac risk and injury, at exacerbation presentation aPWV, serum troponin T, and NT-proBNP were all significantly correlated with each other (aPWV vs. troponin T, rho = 0.421, $P = 0.001$; aPWV vs. NT-proBNP, rho = 0.400, $P = 0.002$; troponin T vs. NT-proBNP, rho = 0.503, $P < 0.001$). In addition, elevated NT-proBNP was associated with higher serum CRP (rho = 0.463; $P < 0.001$) and sputum IL-8 (rho = 0.409; $P = 0.020$).

COPD exacerbations that involved increased sputum purulence had a larger increase from the stable state in serum troponin T concentration than those without increased purulence (0.007 ± 0.009 [n = 26] vs. 0.002 ± 0.005 μg/L [n = 29]; $P = 0.020$).

Longer exacerbations were associated with both greater absolute myocardial injury (serum troponin T) at exacerbation onset, and greater change in troponin T from the stable state (rho = 0.323, $P = 0.027$; rho = 0.390, $P = 0.007$, respectively).

DISCUSSION

Our study informs on the clinically important topic of cardiovascular risk in COPD, the mechanisms of such risk, and the influence of acute exacerbations on these risk markers. We report that arterial stiffness and biomarkers of myocardial injury increase acutely during moderate COPD exacerbations and do not recover for several weeks. The presence of airway infection and preexisting IHD are both associated with greater and more persistent effects. We have also shown that frequent COPD exacerbators have increased arterial stiffness in the stable state. These findings are likely to be of clinical significance given that acute respiratory and cardiovascular events are common and cause substantial morbidity and mortality. Indeed, the

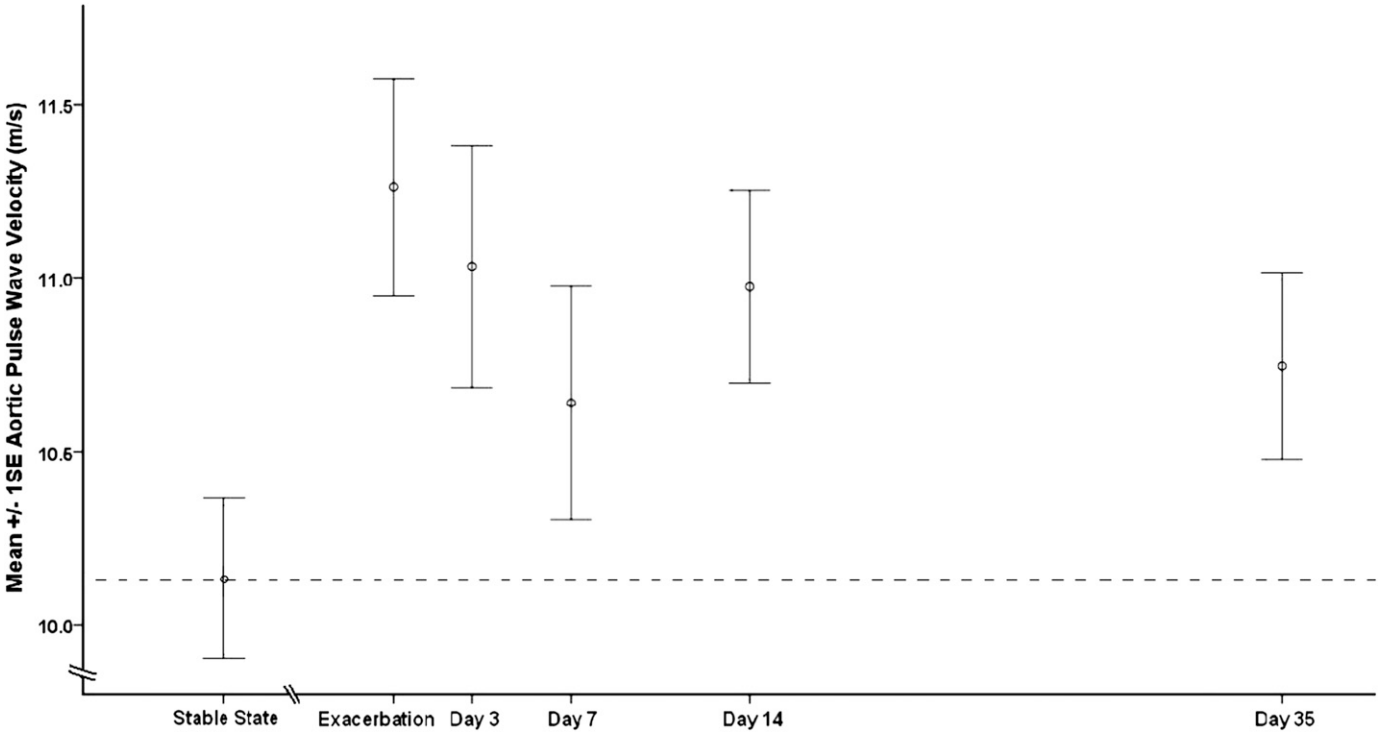

Figure 3. Arterial stiffness falls slowly during recovery from an acute chronic obstructive pulmonary disease exacerbation. Arterial stiffness fell from its peak at exacerbation presentation by an average of 0.017 $ms^{-1}day^{-1}$ (95% confidence interval, 0.001–0.033; $P = 0.040$). Extrapolating this average decline in arterial stiffness during the recovery period indicates a return to the stable-state level at 66 days postexacerbation presentation (95% confidence interval, 33–149 d) (n = 55 at stable state and exacerbation; n = 44 at Day 3; n = 39 at Day 7; n = 38 at Day 14; n = 25 at Day 35; *dotted line* represents mean stable-state aortic pulse wave velocity).

magnitude of differences in arterial stiffness and cardiac biomarkers observed between frequent and infrequent exacerbators and between stable and exacerbated COPD are large enough to be associated with adverse cardiovascular outcomes.

Most COPD exacerbations are treated in primary care, yet previous studies of cardiovascular health during such episodes have focused on hospitalized subjects (15, 28, 29). Using the London COPD Cohort we have been able to prospectively identify and study these more common yet difficult to study moderate events from their early stages, before any systemic therapy, demonstrating deleterious changes in cardiovascular risk and myocardial injury.

Repeated measurements of arterial stiffness in patients with stable COPD were consistent several months apart, thus confirming reliability of this tool, and enabling detection of changes with alterations in clinical status or therapy. Carotid-femoral aPWV is a repeatable, validated gold standard noninvasive marker of cardiovascular risk and mortality, in apparently healthy and disease-specific populations (25). Alternative measures of cardiovascular risk, such as carotid intima-media thickness, are unlikely to mediate acute changes in cardiovascular risk. Arterial stiffness in COPD is known to be higher than in smoking control subjects (21) and related to systemic inflammatory markers, the degree of emphysema, and osteoporosis (30, 31). This suggests a systemic loss of elastic connective tissue over the long-term (32). Our finding that exacerbation frequency status is independently associated with arterial stiffness raises the important possibility that acute exacerbations may accelerate this chronic ongoing process. In our short-term study, we did not find evidence of a step-wise decline in aPWV after exacerbation: there was no difference in paired stable results between patients who did and did not have an intervening exacerbation (data not shown).

We have demonstrated that arterial stiffness is elevated during COPD exacerbations by an average of 1.2 ms^{-1} from the stable state, is independent from changes in blood pressure and heart rate, is higher in the presence of airway infection, and is related to airway inflammation. Increments of 1 ms^{-1} are associated with an increase in cardiovascular events and mortality of 12–18% depending on the risk profile of the population studied (19). Whether a similar magnitude of acute change in an individual relates to a higher or lower degree of cardiovascular risk compared with chronic differences between groups of a similar magnitude remains unknown. Carotid-femoral aPWV improves the Framingham cardiovascular risk prediction independently of standard risk factors (20). Higher arterial stiffness increases myocardial work against elevated systolic aortic pressures and reduces diastolic coronary artery blood flow, which in health is augmented by a slow reflected pulse wave arriving back at the coronary vasculature during diastole (33).

We have shown that clinically significant myocardial injury and dysfunction are common during moderate COPD exacerbations in patients with preexisting IHD. This subpopulation should be a target for future research and intervention during exacerbations. Serum troponin T and NT-proBNP are sensitive and specific markers of myocardial injury and dysfunction, respectively. It is common to find subclinical elevation (>0.03 and >60 pg/ml [>220 pmol/L]) in severe COPD exacerbations requiring hospitalization, where elevated biomarkers are independent predictors of 30-day mortality (15). In our study of less severe (moderate) exacerbations not requiring hospitalization, the prevalence of raised troponin (16.4%) was similar to that in the study by Chang and coworkers (15) (16.6%). In our study, two-thirds of those with a raised troponin at exacerbation did not exceed the threshold in the stable state. However, even

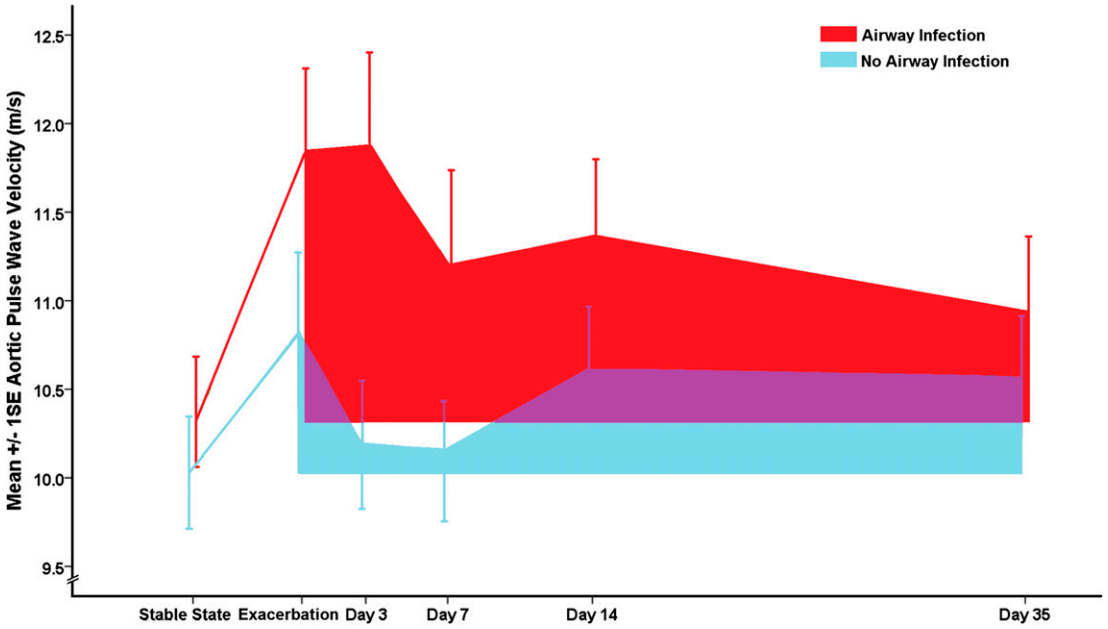

Figure 4. The time course of changes in arterial stiffness during acute and recovery phases of 55 chronic obstructive pulmonary disease exacerbations. Those with airway infection detected at exacerbation (*red*) had a greater and more prolonged rise in arterial stiffness compared with those without detected airway infection (*blue*).

lower levels of troponin elevation during COPD exacerbations may be clinically significant. Hoiseth and colleagues (28) showed that when compared with those with a troponin concentration less than 0.014 μg/L the hazard ratio (95% CI) for death was 4.5 (1.2–16.0) in those with a troponin 0.014–0.04 μg/L and 8.9 (2.4–32.0) in those with a troponin greater than 0.04 μg/L. Elevations of this magnitude are common in ambulatory COPD exacerbations, comprising 29.7% and 12.7% of our sample, respectively, compared with 37.4% and 36.4% in hospitalized exacerbations (26).

The prevalence of a raised NT-proBNP in our ambulatory exacerbations was 16.4% (5.5% in the stable state) when applying the cut-off used by Chang and coworkers (15), compared with their finding of 27.5% in hospitalized patients. Stolz and colleagues (29) have shown that serum BNP fell from a median (IQR) of 65 (34–189) pg/ml at hospital presentation for acute exacerbation to 45 (25–85) pg/ml after 14–18 days. Our data suggest that significant rises in NT-proBNP at exacerbation were limited to those with a history of known IHD. This suggests that management of exacerbations in this subgroup may be improved by additional or alternative cardiac management, although this requires further study.

The mechanisms underlying the links between airway infection, airway and systemic inflammation, increased arterial stiffness, and myocardial injury are not well defined but may include a network of sympathetic nervous system overactivity, nitric oxide bioavailability, and endothelial dysfunction of major arteries. Although increased arterial stiffness in stable COPD is not thought to be mediated by endothelial dysfunction (34), this may be important during exacerbations (35).

Experimental models of human inflammation, such as *Salmonella typhi* vaccination, have been shown to cause endothelial dysfunction (36) and increase arterial stiffness (37), which can be prevented with antiinflammatory therapy, such as high-dose aspirin (38) or simvastatin (39). An ongoing trial of statin therapy is investigating reduction of arterial stiffness in patients with COPD (40). A trial of combined inhaled salmeterol-fluticasone did not show a reduction arterial stiffness in patients with COPD, although a *post hoc* analysis suggested that those in the highest tertile of arterial stiffness may show a response (41). Novel antiinflammatory interventions in COPD are being investigated for a similar effect (42) and could be targeted at high cardiovascular risk patients or pulsed to modulate such risk during acute exacerbations (43).

There may be other mechanisms contributing to increased cardiovascular risk during acute exacerbations, including higher clotting tendency from enhanced platelet activation (16), denser fibrin clots (17), and elevated plasma fibrinogen (18), which is an independent risk factor for IHD (44). Atherosclerotic plaques in elderly patients with COPD are more likely to have a lipid core and may therefore be more vulnerable to rupture (45). Plaque rupture, the precursor to cardiovascular events, is also thought to be more likely in the presence of acute inflammation (46).

To our knowledge, this is the first study to prospectively record increases in arterial stiffness in acute flares of a common chronic inflammatory disease before therapy. Thus, there may be implications for other conditions with acute or chronic inflammation, such as bronchiectasis, inflammatory arthropathies, and bowel diseases. Previous studies have shown decreases in arterial stiffness with antibiotic therapy in cystic fibrosis exacerbations (47) and antiinflammatory therapy in rheumatoid arthritis (48).

We have shown that subclinical myocardial injury is common in moderate COPD exacerbations and this is associated with longer symptom recovery time, in keeping with previous findings (10). This raises questions about the most effective clinical management of such episodes, perhaps with the addition of angiotensin pathway drugs, short-term loop diuretics, or drugs to reduce pulmonary vascular pressure. Clearly such approaches need careful further study.

Regarding limitations of our study, we did not ask patients to fast or stop any medications before clinic visits because we believed it would be unethical to do so during an acute exacerbation. Some medications may have had effects on our measures of cardiovascular risk and myocardial injury; however, these were constant within individuals and changes of chronic medications

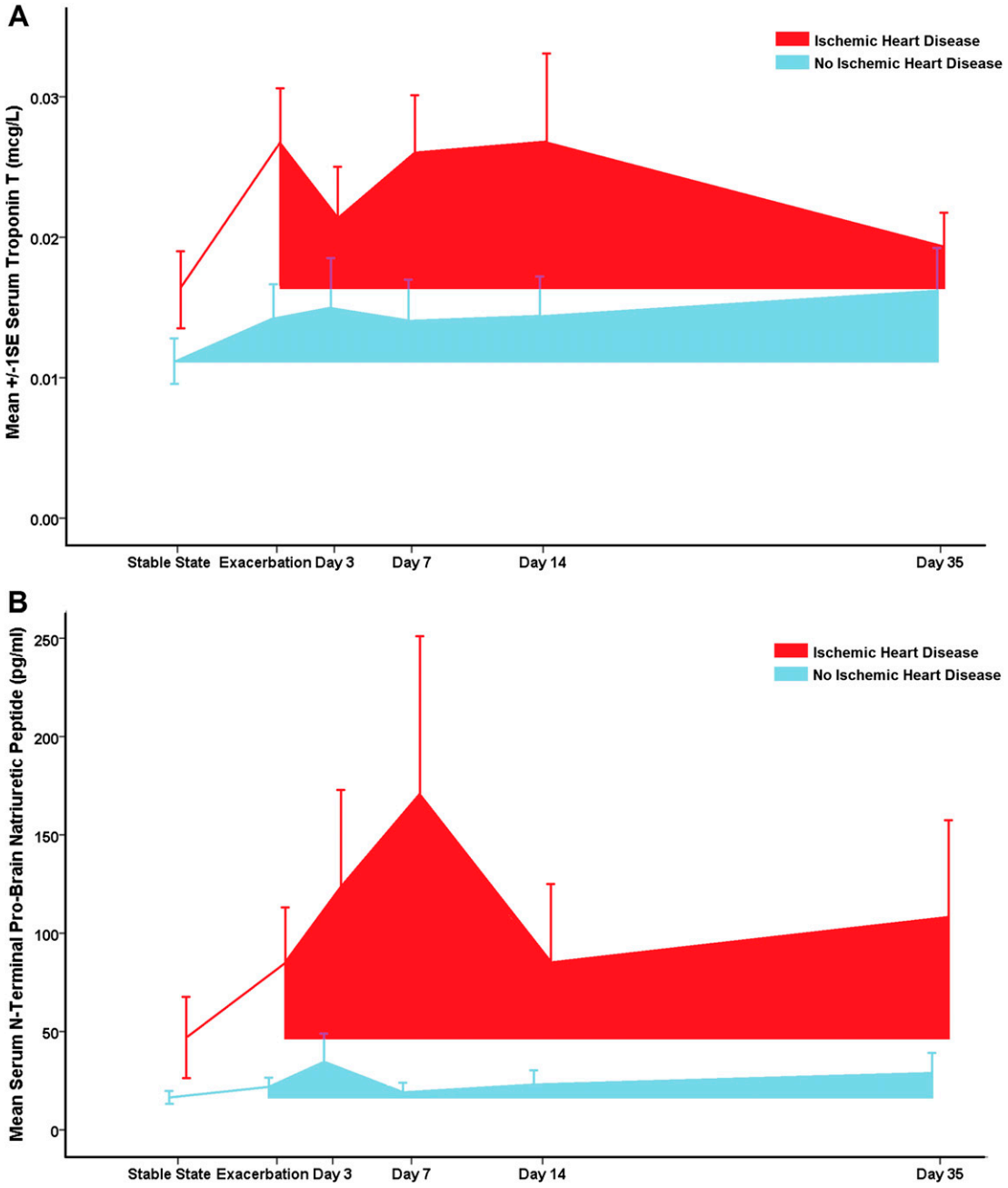

Figure 5. The time course of changes in cardiac biomarkers during acute and recovery phases of 55 chronic obstructive pulmonary disease exacerbations. Those with known ischemic heart disease (*red*) had a higher and more prolonged rise in serum troponin T (*A*) and N-terminal pro–brain natriuretic peptide (*B*) compared with those without ischemic heart disease (*blue*).

were rare between visits. Microbes in sputum detected by PCR do not necessarily always indicate infection; however, in the context of patients with COPD with acute respiratory symptoms, and given the superiority of PCR over other methods (26), we considered this to be the best available criteria for infection at exacerbation. Our definition of airway infection covered the most common pathogens, although we would not have identified all causative bacteria or viruses. However, this would have made it more difficult to demonstrate differences between those with airway infection detected and those without. Finally, because this study was conducted in 55 exacerbations it is possible that we were underpowered to define more subtle relationships between the parameters studied.

In conclusion, in the stable state, frequent COPD exacerbators have greater arterial stiffness than infrequent exacerbators, and this is associated with systemic inflammation. Arterial stiffness also rises acutely during COPD exacerbations and remains elevated for many weeks subsequently. This rise is greater in the presence of airway infection and related to airway inflammation. Myocardial injury and dysfunction are common and clinically significant during COPD exacerbations, particularly in those with underlying IHD, and relate to exacerbation length. Novel approaches to mitigate cardiovascular risk, both in stable COPD and at exacerbation, require further study.

Author disclosures are available with the text of this article at www.atsjournals.org.

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