

# Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk

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## ABSTRACT

**Rationale:** Chronic obstructive pulmonary disease (COPD) is associated with a 2–3-fold increase in the risk of ischaemic heart disease, stroke and sudden death. The mechanisms responsible for this association are not clear and appear to be independent of smoking history.

**Objective:** We test the hypothesis that patients with COPD have increased arterial stiffness and blood pressure in comparison with age and smoking matched controls.

**Methods:** In a prospective case control study, we recruited 102 patients with COPD and 103 healthy controls matched for age and smoking status. Patients were assessed by clinical history and spirometry, with arterial stiffness and blood pressure determined using radial artery applanation tonometry and sphygmomanometry.

**Results:** Patients with COPD had increased arterial stiffness compared with matched controls, with elevated augmentation pressure (17 (1) vs 14 (1) mm Hg;  $p = 0.005$ ) and a reduced time to wave reflection (131 (1) vs 137 (2) ms;  $p = 0.004$ ). These differences were associated with increases in both diastolic (82 (1) vs 78 (1) mm Hg;  $p = 0.005$ ) and systolic blood pressure (147 (2) vs 132 (2) mm Hg;  $p < 0.001$ ). Serum C reactive protein concentrations were threefold higher in patients (6.1 (0.9) vs 2.3 (0.4) mg/l;  $p = 0.001$ ). Data are presented as mean (SEM).

**Conclusions:** Patients with COPD have increased arterial stiffness and blood pressure in comparison with controls matched for age and smoking status. We speculate that increased systemic inflammation and vascular dysfunction could potentially explain the excess cardiovascular morbidity and mortality associated with COPD.

Although primarily a lung disease, chronic obstructive airways disease (COPD) is now recognised to have important systemic consequences that may affect morbidity and mortality.<sup>1</sup> In particular, it is associated with a markedly increased risk of cardiovascular disease.<sup>2</sup> Observational studies suggest that reduced expiratory flow volume (forced expiratory volume in 1 s (FEV<sub>1</sub>)), a characteristic feature of COPD, is associated with a ~3-fold increase in the risk of ischaemic heart disease, stroke and sudden death, with cardiovascular mortality accounting for up to 50% of all deaths in patients with COPD.<sup>3,4</sup> While most patients with COPD are current or ex-smokers, this increased cardiovascular risk is independent of cigarette smoking habit.<sup>2,5</sup>

The mechanisms of increased cardiovascular risk in COPD remain poorly understood. COPD is

characterised by excessive pulmonary inflammation in response to cigarette smoking and air pollution.<sup>6</sup> However, it is increasingly recognised that COPD is also associated with a systemic inflammatory response.<sup>7</sup> During the past 10 years, the role of inflammation and oxidative stress in the pathogenesis of atherosclerosis has been established.<sup>8</sup> The inflammatory mediator C reactive protein (CRP) is an important predictor of cardiovascular outcome in patients with and without coronary artery disease, and has been directly implicated in the pathogenesis of atherosclerotic plaque formation. CRP is increased along with a variety of acute phase proteins in patients with COPD,<sup>9</sup> and may contribute to the development and clinical complications of atherosclerosis in these patients.

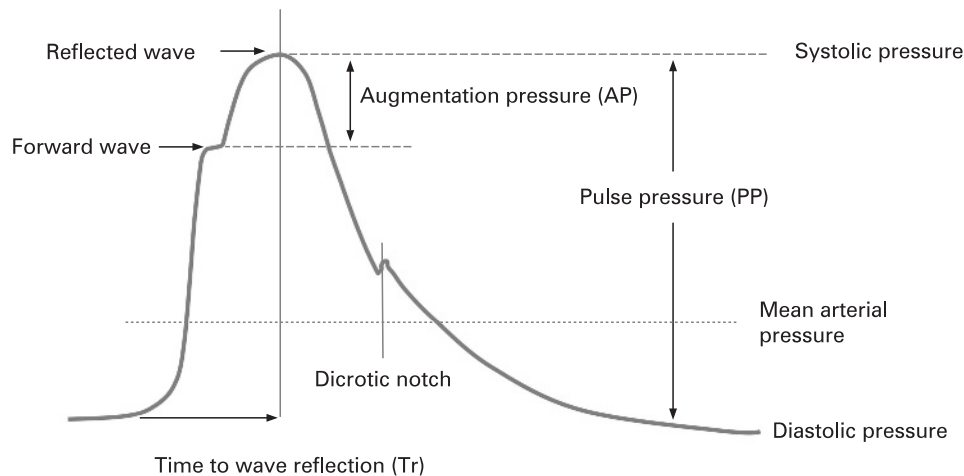
Atherosclerosis is a disease of the large and medium sized elastic arteries in which one of the earliest pathological features is endothelial dysfunction.<sup>10</sup> The vascular endothelium plays an important role in the maintenance of vascular tone through the local release of vasoactive compounds such as nitric oxide. With increasing age and in the presence of cardiovascular risk factors, vascular dysfunction contributes to reduced arterial compliance and increased central arterial pressure.<sup>11</sup> Increased large artery stiffness results in greater central aortic systolic pressures, increased left ventricular afterload and reduced diastolic coronary artery filling. Arterial stiffness may be the central pathological process involved in essential hypertension and is an independent predictor of cardiovascular mortality in these patients.<sup>12</sup>

Applanation tonometry of the radial artery and pulse wave analysis can be used to derive measures of arterial stiffness and central aortic blood pressure. Previously, central arterial stiffness has been linked to reduced FEV<sub>1</sub> in apparently healthy men without coronary heart disease.<sup>13</sup> Increased central arterial stiffness and blood pressure in patients with COPD may explain the excess cardiovascular morbidity and mortality in these patients. In a prospective case control study, we assessed arterial stiffness and blood pressure in patients with COPD and controls matched for age and current smoking status.

## METHODS

### Subjects

Patients with COPD were recruited through general practice databases and a specialised outpatient clinic at the Royal Infirmary of Edinburgh,



**Figure 1** An aortic pulse waveform as produced by the SphygmoCor system from applanation tonometry of the radial artery. Augmentation pressure is the difference between the systolic peak (forward wave) and first systolic inflection (reflected wave) pressures. This difference divided by the pulse pressure generates the augmentation index. Adapted from Smith *et al* 2000.<sup>35</sup>

Edinburgh, UK. COPD was defined by European Respiratory Society/American Thoracic Society guidelines.<sup>14</sup> Patients with a recent exacerbation (within 6 weeks) were excluded. Patients with a history of asthma, bronchiectasis, pulmonary fibrosis, pneumonectomy or pulmonary lobectomy, rheumatoid arthritis, inflammatory bowel disease, connective tissue disorders or malignancy within the previous 5 years and those treated with long term steroids, oral theophylline or immunosuppressive therapy were excluded. Healthy controls were recruited through primary care and were not taking any regular medication. Cases and controls were matched by frequency for age and current smoking status using the mean values for each group. All studies were performed with local ethics approval, written informed consent of all subjects and in accordance with the Declaration of Helsinki.

### Study design

In a prospective case control study, we recruited 102 patients with COPD, and 103 healthy controls matched for age and current smoking status. Subjects were asked to refrain from smoking for 12 h before assessment. Prior to assessment, all medications were withheld for at least 12 h, with long acting

anticholinergic treatment withheld for 24 h. A subgroup of COPD patients with no history of cardiovascular comorbidities was identified. From the history and medical records this group had no prior diagnosis of, and were not on medication for, ischaemic heart disease, hypertension, hypercholesterolaemia or diabetes mellitus. Using the same criteria, control subjects were screened for these cardiovascular risk factors prior to inclusion.

### Pulse wave analysis

Vascular studies were performed in a quiet, temperature controlled room with subjects resting in the supine position. Systolic and diastolic blood pressures were measured in duplicate using a semi-automated non-invasive oscillometric sphygmomanometer, following a 10 min rest period. Pulse wave analysis was performed using micromanometer (Millar Instruments, Texas, USA) applanation tonometry of the radial artery at the wrist and the SphygmoCor system (AtCor Medical, Sydney, Australia), in accordance with the manufacturer's recommendations. Briefly, pulse wave analysis derives an aortic pulse pressure waveform from the radial artery wave via a mathematical transfer function. The arterial pressure waveform is a composite of the forward pressure wave created by ventricular contraction and a reflected wave generated by peripheral vascular resistance (fig 1).<sup>15</sup> The augmentation index, which is the difference between the second and first systolic peaks expressed as a percentage of the pulse pressure, is a measure of systemic arterial stiffness and wave reflection. The time to wave reflection (Tr) is reduced with increasing arterial stiffness, and provides a surrogate of aortic pulse wave velocity.<sup>16</sup>

At least two independent waveform analyses were obtained from each subject, with measurements only accepted on meeting SphygmoCor quality control criteria. These replicate measures of augmentation pressure were highly correlated across the study population ( $r = 0.939$ ,  $p < 0.0001$ ,  $n = 205$ ). Measurements were performed by staff specifically trained in the technique and blinded to the clinical characteristics of each subject.

### Assays

Differential white blood cell count and platelets were determined using an autoanalyser. Serum lipid profile was determined by the regional accredited clinical biochemistry

**Table 1** Baseline characteristics of patients with chronic obstructive pulmonary disease and matched healthy controls

|                                      | Healthy controls<br>(n = 103) | COPD patients<br>(n = 102) | p Value |
|--------------------------------------|-------------------------------|----------------------------|---------|
| Sex (M/F)                            | 51/52                         | 61/41                      | 0.161   |
| Age (y)                              | 66.7 (0.7)                    | 67.1 (0.7)                 | 0.677   |
| Current smoker                       | 49 (48)                       | 48 (47)                    | 1.000   |
| Ex-smoker                            | 54 (52)                       | 54 (53)                    | 1.000   |
| Serum total cholesterol (mmol/l)     | 5.5 (0.1)                     | 5.7 (0.1)                  | 0.329   |
| LDL cholesterol (mmol/l)             | 3.2 (0.1)                     | 3.1 (0.1)                  | 0.444   |
| HDL cholesterol (mmol/l)             | 1.5 (0.1)                     | 1.6 (0.1)                  | 0.335   |
| C reactive protein (mg/l)            | 2.3 (0.4)                     | 6.1 (0.9)                  | 0.001   |
| Height (cm)                          | 168 (0.9)                     | 164 (2.3)                  | 0.097   |
| Weight (kg)                          | 76 (1.3)                      | 69 (2.2)                   | 0.005   |
| Body mass index (kg/m <sup>2</sup> ) | 27 (0.4)                      | 25 (0.7)                   | 0.014   |

Values are mean (SEM) or number (%).

Significance (p): unpaired t test (continuous variables),  $\chi^2$  (categorical data).

COPD, chronic obstructive pulmonary disease; HDL, high density lipoprotein; LDL, low density lipoprotein.

**Table 2** Baseline characteristics of patients with chronic obstructive pulmonary disease with and without established cardiovascular comorbidities

|                                      | COPD with CV comorbidity (n = 47) | COPD without CV comorbidity (n = 55) | p Value |
|--------------------------------------|-----------------------------------|--------------------------------------|---------|
| Sex (M/F)                            | 28/19                             | 33/22                                | 1.00    |
| Age (y)                              | 67.3 (1.0)                        | 66.9 (1.0)                           | 0.217   |
| Current smoker                       | 19 (40)                           | 29 (53)                              | 0.238   |
| Ex-smoker                            | 28 (60)                           | 26 (47)                              | 0.238   |
| Serum total cholesterol (mmol/l)     | 5.5 (0.2)                         | 5.8 (0.1)                            | 0.118   |
| LDL cholesterol (mmol/l)             | 2.9 (0.2)                         | 3.2 (0.2)                            | 0.376   |
| HDL cholesterol (mmol/l)             | 1.4 (0.1)                         | 1.7 (0.1)                            | 0.670   |
| C reactive protein (mg/l)            | 6.8 (1.7)                         | 5.4 (0.7)                            | 0.115   |
| Height (cm)                          | 162 (3.0)                         | 165 (3.4)                            | 0.982   |
| Weight (kg)                          | 70 (3.2)                          | 69 (3.0)                             | 0.756   |
| Body mass index (kg/m <sup>2</sup> ) | 26 (1.1)                          | 24 (0.8)                             | 0.092   |

Values are mean (SEM) or number (%).

Significance (p) unpaired t test or  $\chi^2$ .

COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HDL, high density lipoprotein; LDL, low density lipoprotein.

laboratory. Serum CRP concentrations were measured using a highly sensitive immunonephelometric assay (Behring BN II nephelometer, Marburg, Germany).

### Data analysis and statistics

Data were analysed using SPSS (V.14). Comparisons were made between patients with COPD and matched controls using unpaired t tests for continuous variables and  $\chi^2$  analysis for categorical data. Comparisons were made between controls and the two pre-specified COPD subgroups, those patients with or without a history of cardiovascular comorbidities, using analysis of variance (ANOVA). Correlations between hsCRP and measures of arterial stiffness were analysed in patients with COPD and controls using the Pearson's correlation coefficient. Continuous variables were reported as mean (SEM) and statistical significance was taken at  $p < 0.05$ .

### RESULTS

The populations were matched for age and current smoking status (table 1). In patients with COPD, mean post-bronchodilator

FEV<sub>1</sub> was 46 (2)% predicted, post-bronchodilator FVC 68 (2)% predicted and FEV<sub>1</sub>/FVC ratio 50 (1)% predicted. When stratified by Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage, 2% of patients were stage I, 36% stage II, 39% stage III and 20% stage IV. While well matched for current smoking status, there was a modest yet significant difference between patients and controls (46 (2) vs 33 (2) pack years;  $p = 0.004$ ). Weight ( $p = 0.005$ ) and body mass index ( $p = 0.014$ ) were reduced in patients with COPD compared with healthy controls. In patients with COPD, lipid profiles were similar in the presence or absence of established cardiovascular comorbidities. Serum CRP concentrations were higher in the COPD groups than in controls ( $p = 0.001$ ).

The two pre-specified COPD subgroups, those patients with or without a history of cardiovascular comorbidities, were well matched (table 2). Patients with COPD had increased arterial stiffness compared with matched controls (table 3), with elevated augmentation pressures (17 (1) vs 14 (1) mm Hg;  $p = 0.015$ ) (fig 2) and a reduced time to wave reflection (131 (1) vs 137 (2) ms;  $p = 0.005$ ) (fig 3). These relationships remained significant in the COPD subgroup with no history of cardiovascular comorbidities. Consistent with increased arterial stiffness, these differences were associated with increases in both systolic (147 (2) vs 132 (2) mm Hg;  $p < 0.001$ ) and diastolic (82 (1) vs 78 (1) mm Hg;  $p = 0.007$ ) blood pressure. Serum CRP concentrations were threefold higher in patients than in controls (6.0 (0.9) vs 2.3 (0.4) mg/l;  $p = 0.001$ ) (fig 4). Serum CRP concentrations correlated with augmentation pressure in patients with COPD ( $r = 0.736$ ,  $p = 0.034$ ) but not in controls ( $r = -0.154$ ,  $p = 0.21$ ).

### DISCUSSION

Patients with COPD have increased arterial stiffness, blood pressure and systemic inflammation in comparison with controls matched for age and current smoking status. These differences are not caused by the presence of comorbidity in patients with COPD as arterial stiffness and pressure measurements were similar in the subgroup of patients without existing ischaemic heart disease, hypertension, hypercholesterolaemia or diabetes mellitus. These findings provide a plausible mechanism for the increased cardiovascular morbidity and mortality associated with COPD.

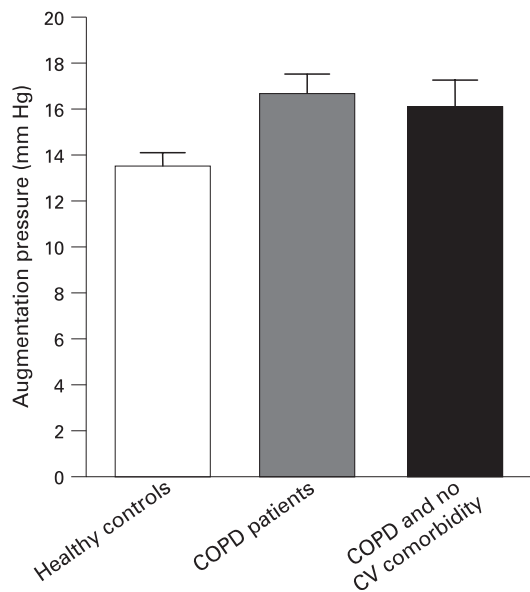
**Table 3** Arterial stiffness and blood pressure in patients with chronic obstructive pulmonary disease and matched healthy controls

|                               | Healthy controls (n = 103) | COPD with CV comorbidity (n = 47) | COPD without CV comorbidity (n = 55) | p Value |
|-------------------------------|----------------------------|-----------------------------------|--------------------------------------|---------|
| Heart rate (bpm)              | 67 (1)                     | 69 (2)                            | 69 (2)                               | 0.621   |
| Peripheral sBP (mm Hg)        | 132 (2)                    | 149 (3.5)                         | 146 (3)                              | 0.000   |
| Peripheral dBP (mm Hg)        | 78 (1)                     | 82 (2)                            | 83 (2)                               | 0.019   |
| Peripheral MAP (mm Hg)        | 96 (1)                     | 105 (2)                           | 104 (2)                              | 0.000   |
| Peripheral PP (mm Hg)         | 54 (1)                     | 68 (3)                            | 63 (2)                               | 0.000   |
| Central sBP (mm Hg)           | 123 (2)                    | 137 (3)                           | 134 (3)                              | 0.000   |
| Central dBP (mm Hg)           | 79 (1)                     | 83 (2)                            | 84 (2)                               | 0.011   |
| Central MAP (mm Hg)           | 99 (1)                     | 105 (2)                           | 104 (2)                              | 0.045   |
| Central PP (mm Hg)            | 45 (1)                     | 54 (3)                            | 51 (2)                               | 0.001   |
| Augmentation pressure (mm Hg) | 14 (1)                     | 17 (1)                            | 16 (1)                               | 0.016   |
| Augmentation index (%)        | 30 (1)                     | 31 (2)                            | 31 (1)                               | 0.628   |
| Time to reflection (ms)       | 137 (2)                    | 131 (2)                           | 131 (2)                              | 0.015   |

Values are mean (SEM).

Groups compared with ANOVA.

COPD, chronic obstructive pulmonary disease; dBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; sBP, systolic blood pressure.



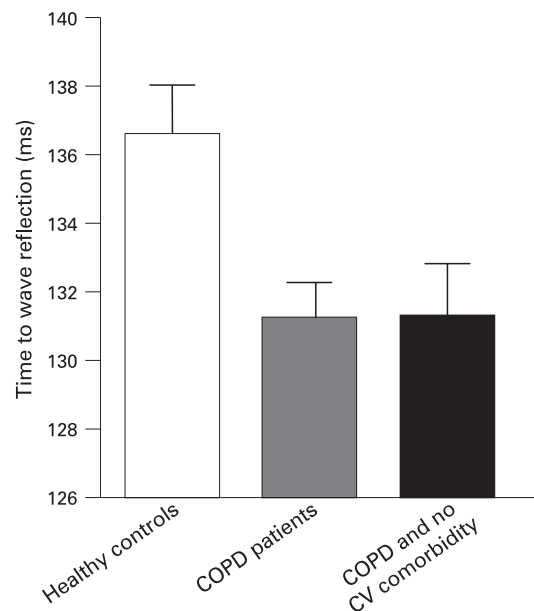
**Figure 2** Mean augmentation pressure, a measure of arterial stiffness, was greater in patients with chronic obstructive pulmonary disease (COPD) ( $p = 0.005$ ) and the subgroup of patients with COPD and no cardiovascular (CV) comorbidity ( $p = 0.04$ ) compared with healthy controls matched for age and current smoking status.

#### Arterial stiffness

Increased large artery stiffness in patients with COPD was associated with higher peripheral systolic and diastolic blood pressures. While a number of factors may influence arterial tone and blood pressure in these patients, it is possible that increased large artery stiffness is the major determinant of increased blood pressure and hence cardiovascular risk in patients with COPD. Recently it has been established that measures of arterial stiffness, including augmentation and central pulse pressure, independently predict adverse clinical outcome in patients with hypertension.<sup>17</sup>

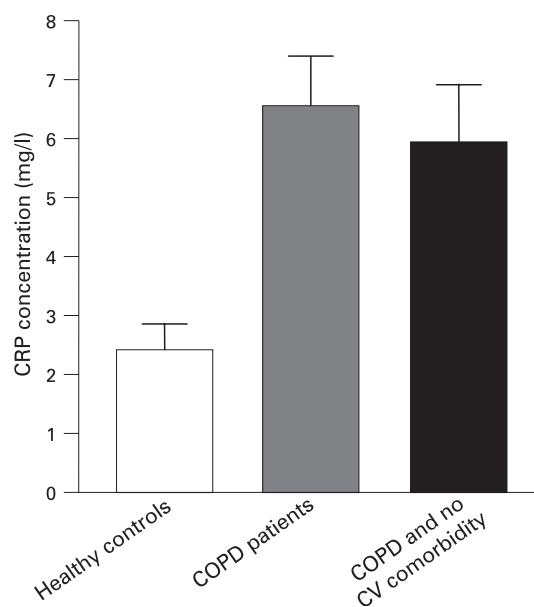
Arterial stiffness is influenced by both structural and functional aspects of the conduit arteries and resistance beds. Atherosclerosis and calcification of the large arteries decreases vascular compliance, and structural changes in the vessel wall may explain the increased arterial stiffness observed in patients with COPD. Arterial stiffness and calcification increases with age. The average age of our patients was 67 years and yet augmentation pressures were similar to those of a healthy group of 80 year olds, suggesting that COPD may result in premature ageing of the vasculature.<sup>11</sup> Augmentation pressures in patients with COPD were greater than those of a similar aged population with documented coronary artery disease.<sup>18</sup> Consistent with this hypothesis, cigarette smoking and impaired lung function are associated with premature ageing and morphological abnormalities in the dermis with reduced elastic fibre content.<sup>19</sup> It is possible that excessive neutrophil elastase activity in cigarette smokers and patients with COPD<sup>5, 20</sup> results in consumption of elastic fibres in the media of the large arteries leading to arterial stiffness.

Arterial stiffness is also determined by the functional properties of the vessel wall with endothelium dependent vasomotor tone involved in the dynamic modulation of augmentation pressure.<sup>21, 22</sup> There is extensive evidence of endothelial dysfunction in cigarette smokers and in patients with atherosclerosis.<sup>23, 24</sup> Whether COPD causes an additional impairment of systemic endothelial dysfunction is not yet known. However,



**Figure 3** Mean time to wave reflection was reduced in patients with chronic obstructive pulmonary disease (COPD) ( $p = 0.004$ ) and the subgroup of patients with COPD and no cardiovascular (CV) comorbidity ( $p = 0.03$ ) compared with healthy controls matched for age and current smoking status.

local inflammation is associated with endothelial dysfunction in the pulmonary vasculature<sup>25</sup> and it seems likely that similar processes may influence the extra-pulmonary vasculature. Using *Salmonella typhus* vaccination as a model of acute systemic inflammation, recent work suggests that inflammation can acutely increase aortic stiffness.<sup>26</sup> This model has also been shown to transiently but profoundly alter systemic endothelial function.<sup>27</sup> Interestingly, Kampus *et al* demonstrated that serum CRP concentrations are positively correlated with indices of arterial stiffness in healthy individuals.<sup>28</sup>



**Figure 4** Mean serum C reactive protein (CRP) concentrations were increased in patients with chronic obstructive pulmonary disease (COPD) in the presence or absence of established cardiovascular (CV) comorbidity ( $p = 0.001$  for both).



Serum CRP concentrations were elevated in our patients and similar findings have been reported in other published COPD cohorts.<sup>9–29</sup> We hypothesise that systemic inflammation and vascular dysfunction may be responsible for our findings of increased blood pressure and arterial stiffness in COPD. The COPD patients in our cohort had a lower body mass index than healthy controls. This is a recognised feature of COPD and is likely to be a result of persistent bronchial and systemic inflammation.<sup>1</sup> Serum CRP concentrations correlated with augmentation pressure in patients with COPD, but not in matched controls.

### Hypertension

Our findings emphasise the need for better monitoring and treatment of traditional cardiovascular risk factors in patients with COPD. Based on the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure guidelines,<sup>30</sup> two-thirds of our COPD population had blood pressures compatible with a diagnosis of hypertension, compared with just one-third of age matched controls. These findings are in keeping with a recently published prospective cohort study in which the prevalence of hypertension was approximately 50% in 5648 patients with COPD.<sup>31</sup> Observational studies indicate that death from ischaemic heart disease and stroke increases linearly with blood pressure in all age groups.<sup>32</sup> For every 20 mm Hg systolic or 10 mm Hg diastolic increase in blood pressure, there is a doubling of cardiovascular mortality. A number of factors in addition to increased arterial stiffness may be responsible for the hypertension observed in patients with COPD.

### Study limitations

One potential limitation in our study design is that many of the patients with COPD were recruited from a tertiary referral centre. This may have introduced some bias towards increased comorbidity that could potentially explain the observed differences between patients and controls. In order to counter this potential bias, we undertook a subgroup analysis in which patients with ischaemic heart disease and previously recognised cardiovascular risk factors were excluded. Differences in arterial stiffness and blood pressure persisted even when these patients were excluded.

While patients with COPD were characterised carefully with spirometry and reversibility, lung function was not measured in the healthy control group. It is possible that a minority of asymptomatic smokers had undiagnosed airways obstruction, although if anything inclusion of these subjects would be likely to reduce any important differences between the two groups. While we carefully matched patients with controls to ensure an equal balance of current smokers and ex-smokers to avoid the well established vascular and inflammatory effects of active smoking, there were differences in the number of pack years smoked between the cohorts. It is difficult to control fully for the cumulative effects of cigarette smoke in a case control study, as an abnormal inflammatory response in the lungs to cigarette smoke is central to the pathogenesis of COPD. Cigarette smoke has a well documented acute effect on blood pressure and arterial stiffness<sup>33</sup> and both are increased in current smokers compared with non-smokers.<sup>34</sup> However, a relationship between arterial stiffness or blood pressure and the magnitude of previous cigarette exposure (pack years) has not been established. We found no association between pack years smoked and any of the vascular parameters measured, and do

not believe that small differences in past cigarette exposure account for the reported differences in vascular function between COPD patients and controls.

### CONCLUSIONS

Patients with COPD have increased arterial stiffness, blood pressure and systemic inflammation. We hypothesise that systemic inflammation and vascular dysfunction may explain the excess cardiovascular morbidity and mortality associated with COPD. Further research into the mechanisms responsible for the increase in arterial stiffness is warranted. Increased awareness and targeted treatment of cardiovascular risk and hypertension has the potential to reduce morbidity and improve prognosis in COPD.

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**Competing interests:** None.

**Ethics approval:** All studies were performed with local ethics approval.

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## Lung alert

### HIF1 $\alpha$ in hypoxia

Conjugation of small ubiquitin-related modifier proteins (SUMO) to form larger substrates has been implicated in the regulation of multiple cellular processes in mammals including transcription, cell signalling and cancer progression. This conjugation is a dynamic process that can be reversed by a family of Sentrin/SUMO-specific proteases (SENPs).

This study investigated the physiological consequences of SUMOylation and deSUMOylation with particular regard to hypoxia-inducible factor 1 $\alpha$  (HIF1 $\alpha$ ) and SENP1. A series of experiments were undertaken using SENP1 (a nuclear SUMO protease) knockout mice (SENP1<sup>-/-</sup>). SENP1 was chosen as earlier studies implicated SENP1 mutations in early fetal death in mice and SENP1 is found in humans.

By comparing SENP1<sup>-/-</sup> and SENP1 wild-type mice (SENP1<sup>+/-</sup>), it was established that mid gestation fetal death occurred secondary to severe fetal anaemia because of deficient erythropoietin production. Erythropoietin production was subsequently linked with the stability of HIF1 $\alpha$ , a process that was directly influenced by the presence of SENP1. Hypoxia-induced SUMOylation and subsequent degradation of HIF1 $\alpha$  is increased in SENP1<sup>-/-</sup> mice compared with wild-type mice, which suggests that SENP1 is essential to prevent degradation of HIF1 $\alpha$  in response to hypoxia. Further experimentation showed that the degradation of HIF1 $\alpha$  was through a Von Hippel-Lindau and ubiquitin/proteasome dependent mechanism.

This study highlights the important biological consequences that SUMOylation and deSUMOylation can have in mammals. In particular, the presence of SENP1 is essential to stabilise HIF1 $\alpha$  in response to hypoxia for prevention of early fetal death in mice. The study does not identify why hypoxia causes SUMOylation of HIF1 $\alpha$  and further studies are required to establish the nature of this.

- Cheng J, Kang X, Zhang S, *et al.* SUMO-specific protease 1 is essential for stabilisation of HIF1 $\alpha$  during hypoxia. *Cell* 2007;**131**:584–95

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