Traditional and emerging indicators of cardiovascular risk in chronic obstructive pulmonary disease

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Abstract

With the increased cardiovascular (CV) morbidity and mortality in subjects with chronic obstructive pulmonary disease (COPD), there is a priority to identify those patients at increased risk of cardiovascular disease. Stable patients with COPD ($n = 185$) and controls with a smoking history ($n = 106$) underwent aortic pulse wave velocity (PWV), blood pressure (BP) and skin autofluorescence (AF) at clinical stability. Blood was sent for fasting lipids, soluble receptor for advanced glycation end products (sRAGE) and CV risk prediction scores were calculated. More patients (18%) had a self-reported history of CV disease than controls (8%), $p = 0.02$, whilst diabetes was similar (14% and 10%), $p = 0.44$. Mean (SD) skin AF was greater in patients: 3.1 (0.5) AU than controls 2.8 (0.6) AU, $p < 0.001$. Aortic PWV was greater in patients: 10.2 (2.3) m/s than controls: 9.6 (2.0) m/s, $p = 0.02$ despite similar BP. The CV risk prediction scores did not differentiate between patients and controls nor were the individual components of the scores different. The sRAGE levels were not statistically different. We present different indicators of CV risk alongside each other in well-defined subjects with and without COPD. Two non-invasive biomarkers associated with future CV burden: skin AF and aortic PWV are both significantly greater in patients with COPD compared to the controls. The traditional CV prediction scores used in the general population were not statistically different. We provide new data to suggest that alternative approaches for optimal CV risk detection should be employed in COPD management.

Keywords

Cardiovascular risk, COPD, advanced glycation end products, aortic stiffness, autofluorescence

Introduction

The increased cardiovascular (CV) risk in patients with chronic obstructive pulmonary disease (COPD) has been the subject of great research interest, particularly as it is an important cause of the excess morbidity and mortality in patients compared to people without COPD.[1,2] However, routinely assessing CV state, predicting CV risk or considering primary preventative strategies in patients with COPD are not part of guidelines and are not routinely performed in clinical practice, no doubt in part as the optimal method remains uncertain.

In the general population, CV risk prediction scores can assess the likelihood of future CV events or mortality.[3,4] There are caveats in that they are not universally performed[5] and are not applicable for people with pre-existent CV disease and some are not suitable for those with diabetes mellitus; these other conditions in themselves influence future CV risk

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greater. Further, in certain disease states such as rheumatoid arthritis, modification of the CV risk prediction algorithm has been required to enhance their prognostication.[6] Despite these considerations, they are a standard method for detecting risk in the community population. Of importance though, there is growing awareness that multimorbidity might require a fresh approach to assessment and management, where traditional risk factors are combined with other less identified factors that enhance risks.[7,8] The utility of the traditional CV risk prediction scores in patients with COPD has not been assessed.

Alternative methods for determining CV risk have been proposed. Several studies have consistently reported increased aortic stiffness in patients with COPD compared to age- and gender-matched controls with a smoking history.[9,10] Aortic stiffness, using aortic pulse wave velocity (PWV) is an independent predictor of CV disease in this age group of subjects but is not, as yet, a clinical measure in everyday practice.[11,12] Aortic stiffness adds to the traditional CV risk factors in predicting risk in the Framingham cohort.[13]

The contribution of advanced glycation end products (AGE; markers of glycaemic and oxidative stress, pro-inflammatory and altering structure through collagen cross-linking), its receptor (RAGE) and the soluble decoy receptor: sRAGE in COPD pathology have been studied recently.[14–18] Skin autofluorescence (AF) permits a non-invasive measurement of skin AGE and has been validated against the skin biopsy gold standard.[19] Skin AF reflects tissue accumulation of oxidative stress, unlike circulating AGE levels that are more variable, affected by diet[20] and crucially in a lung disease such as COPD, by smoking.[21] In patients with COPD, skin AF is increased compared to controls[22] and there are age-related increases.

Skin AF has been associated with CV and renal risk factors[23] and reported as a useful clinical adjunct when evaluating both fatal and non-fatal CV events, and total mortality in different populations.[24–26] Associations between skin AF and cardiovascular risk measures such as arterial stiffness in patients with end-stage renal disease have been reported.[27] Low sRAGE is associated with future CV disease,[28] whilst the tissue receptor for AGE has been implicated in structural vascular wall changes and a role in atherosclerosis.[29]

We set out to assess CV risk parameters in well-characterized patients with COPD and controls with a smoking history using multiple approaches, including currently recognised CV risk scores used in the general population and other emerging indicators including aortic stiffness and skin AF. Here, we report the different approaches alongside each other for the first time in COPD.

Methods

Subjects

Consenting patients with confirmed COPD[30] ($n = 185$) and gender-matched controls free from respiratory disease and symptoms ($n = 106$) were recruited during 2011–2013 from volunteer databases, outpatient clinics and by advertisement. All subjects were over 40 years of age, of European descent, had a smoking history of greater than 10 pack-years and were studied at clinical stability. All subjects gave written informed consent and the study was approved by the National Research Ethics Committee (10/H0406/65). No one had active or suspected malignancy, terminal disease or known α1 antitrypsin deficiency.

Cardiovascular measurements

Patients were asked to refrain from short-acting bronchodilators for a minimum of 4 hours and long-acting bronchodilators for >12 hours prior to the study. All subjects were asked to refrain from caffeine products for >6 hours. Tests were performed after a period of resting supine for >10 minutes. Heart rate (HR) and peripheral blood pressure (BP) were performed in the seated position and the mean of two technically acceptable results was recorded (Omron 705IT, UK). Pulse pressure (PP) and mean arterial pressure (MAP) were calculated. Aortic PWV was performed using Vicorder (Skidmore Medical, UK) using a thigh cuff to measure femoral pulse and a partial cuff around the neck at the level of the carotid artery. Sequentially recorded carotid and femoral artery waveforms allowed calculation of wave transit time. Aortic PWV was determined by dividing path length by wave transit time, which was measured in triplicate and the average recorded.[31]

Anthropometry and lung function

Height and weight were measured (Seca, Germany) and body mass index (BMI) calculated. Fat-free mass (FFM) was calculated using bioelectrical impedance analysis (Tanita 418, Japan). A height-squared FFM index (FFMI) was calculated.

Post-bronchodilator spirometry was performed (Microlab MK6, Micromedical, UK) to determine forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC). Oxygen saturations after 10 minutes rest (Konica Minolta Pulsox-300) breathing air and exhaled carbon monoxide levels were performed (Clement Clarke International, UK).

Biochemistry

Venous blood was taken for fasting lipids. Lipid profile analytes were measured on the Olympus AU2700 platform (Beckman Coulter, Brea, California, USA). Estimated glomerular filtration rate (eGFR) was calculated.[32] Serum was centrifuged, aliquoted and stored at $-80°C$ for later determination of circulating sRAGE (R&D systems, UK) by enzyme-linked immunosorbent assay in duplicate.

Other measurements

Detailed medical, medication and smoking history were recorded. Past medical history was collected by detailed questioning to the patient and patient consent for access to Trust medical records. The COPD assessment tool (CAT) and St George's Respiratory Questionnaire (SGRQ) were completed.[33,34]

Cardiovascular risk scores

Cardiovascular risk scores were calculated to determine the risk of a CV event in the next 10 years using the National Heart, lung, Blood Institute (NHLBI)[3] and American College of Cardiology/American Heart Association (ACC/AHA)[4] equations. The NHLBI is not suitable for subjects with ischaemic heart disease (IHD) or diabetes and therefore was performed on a subgroup. The ACC/AHA calculator permits inclusion of diabetics but is not suitable for those with IHD, therefore again performed on a (different) subgroup.

Statistics

Data were analysed using Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA) version 21.0. The main analyses compared skin AF and aortic stiffness between the patients with COPD and controls using independent t-tests.

At recruitment, we purposely did not exclude subjects with co-existent IHD or diabetes mellitus. This was in order to represent clinical practice as much as possible. However, we opted a priori to compare the key variables between patients with COPD and controls in the subgroup without evidence of IHD or diabetes. Further, as above, the CV risk score calculations were only possible in subgroups.

Normally distributed data were presented as mean and SD and where possible, non-normally data (e.g. sRAGE) was $\log_{10}$ transformed in order to perform parametric analysis and presented as geometric mean and SD. Non-parametric tests were performed on age, smoking pack-years and carbon monoxide, with results presented as median and interquartile range. Chi-squared test was used to compare categorical data between groups, including gender and smoking status. A $p < 0.05$ was considered significant.

Multiple stepwise linear regression was performed to adjust analyses for accepted confounders such as age and gender where appropriate. The association between skin AF and other key variables were assessed in a multiple forward linear regression in patients. Independent variables of interest were entered if significant at the $p < 0.1$ level in univariate analysis. The skin AF was the dependent variable and the independent variables of age, gender, $FEV_1\%$ predicted, presence of IHD and diabetes entered into the model.

A power calculation indicated that to determine a 10% difference in skin AF between patients with COPD and controls, with 90% power and a SD of 0.5 arbitrary units (AU), 292 subjects were required. This would also give >90% power to detect a 10% difference in aortic PWV between groups with a SD of 2.2 m/s and provide over 99% power at the 5% significance level to detect a 0.2 AU difference in AF per 10% increase $FEV_1\%$ predicted, assuming linear effects.

Results

Demographic data including gender proportion and BMI were similar between patients with COPD and controls, as shown in Table 1. The patients were marginally older. Resting oxygen saturations breathing air were <92% in 13 patients with COPD but not in controls. There were significantly more patients (18%) with self-reported IHD compared to controls (8%), $p = 0.02$; and 14% of patients and 10% controls with diabetes, $p = 0.44$, as shown in Table 2.

CV risk scores are not significantly greater in patients with COPD compared to controls

The CV risk scores were performed where eligible: the NHLBI risk score was performed in 132 patients

Table 1. Demographics of study population.[a]

	COPD (n = 185)	Control (n = 106)	p Value
Age (years)[b]	68 (57–79)	66 (54–78)	0.04
Gender (male n %)	116 (63)	65 (61)	0.87
Smoking status % current	30%	21%	0.09
Smoking pack-years (pack-years)[b]	42 (15–69)	23 (13–49)	<0.001
FEV_1 (l)	1.6 (0.6)	2.8 (0.7)	<0.001
FEV_1% predicted (%)	58 (18)	100 (14)	<0.001
FEV_1/FVC ratio	49 (13)	74 (7)	<0.001
Resting oxygen saturations (%)[b]	95 (94–96)	96 (95–97)	<0.001
Carbon monoxide (ppm)[b]	3 (1–13)	2 (1–6)	0.0661
CAT score	19 (9)	7 (6)	<0.001
SGRQ total score	40 (21)	8 (9)	<0.001
BMI (kg/m^2)	27.2 (5.5)	27.8 (4.6)	0.32
FFMI (kg/m^2; 175 patients, 102 controls)	18.4 (2.8)	18.9 (2.3)	0.12

BMI: body mass index; CAT: COPD assessment test; FEV_1: forced expired volume in 1 second; FEV_1/FVC: forced expired volume in 1 second to forced vital capacity ratio; FFMI: fat-free mass index; SGRQ: St George's Respiratory Questionnaire.
[a]Presented as mean and SD unless otherwise stated.
[b]median (inter-quartile range),

Table 2. Self-reported comorbidities and medications.[a]

	COPD (n = 185)	Control (n = 106)	p Value
IHD n (%)	33 (18)	8 (8)	0.02
Diabetes n (%)	25 (14)	11 (10)	0.44
Statins n (%)	71 (38)	32 (30)	0.21
Other antihypertensive/CV medication n (%)	81 (44)	34 (32)	0.09
ICS n (%)	117 (63)	0	

CV: cardiovascular; IHD: ischaemic heart disease; ICS: inhaled corticosteroids.
[a]Other CV medication included beta blockers, ACE inhibitors, angiotensin receptor blockers and calcium channel blockers

Table 3. Haemodynamic status and cardiovascular risk scores.

Mean (SD) unless otherwise indicated	COPD (n = 185)	Control (n = 106)	p Value
Skin AGE (AU)	3.1 (0.5)	2.8 (0.6)	<0.001
Aortic PWV (m/s)	10.2 (2.3)	9.6 (2.0)	0.02
Peripheral systolic BP (mmHg)	146 (22)	146 (17)	0.95
Peripheral diastolic BP (mmHg)	84 (11)	85 (11)	0.74
Peripheral PP (mmHg)	62 (17)	61 (14)	0.90
Peripheral MAP (mmHg)	105 (13)	105 (12)	0.82
HR (bpm)	75 (15)	71 (12)	0.01
Central PP (mmHg)	58 (17)	58 (13)	1.0
Central MAP (mmHg)	110 (14)	111 (12)	0.67
Total cholesterol (mmol/L)	5.1 (1.2)	5.3 (1.2)	0.13
LDL cholesterol (mmol/L)	2.7 (1.0)	2.9 (1.0)	0.16
HDL cholesterol (mmol/L)	1.7 (0.5)	1.6 (0.4)	0.32
sRAGE (pg/mL)[a]	949.9 (1.7)	1057.1 (1.6)	0.09
eGFR (mL/min)	70 (14)	73 (12)	0.24
ACC/AHA CV risk score (COPD n = 152, controls n = 98)	20.2 (13.5)	17.4 (12.7)	0.09
NHLBI CV risk score (COPD n = 132, controls n = 88)	10.9 (7.8)	10.3 (7.9)	0.54

PP: pulse pressure; ACC/AHA: American College of Cardiology/American Heart Association; BP: blood pressure; eGFR: estimated glomerular filtration rate; MAP: mean arterial pressure; NHLBI: National Heart, Lung and Blood Institute; PWV: pulse wave velocity; sRAGE: soluble receptor for AGE; AGE: advanced glycation end products; COPD: chronic obstructive pulmonary disease; HR: heart rate.
[a]Geometric mean.

There were no significant differences between patients and controls for any of the individual components of the CV risk scores including BP, total or HDL–cholesterol, current smoking status or proportion on antihypertensive or other CV medication.

Skin AF is elevated in patients with COPD

The mean (SD) skin AF was greater in patients with COPD, 3.1 (0.5) AU, compared with controls, 2.8(0.6), $p < 0.001$ and remained significant after adjusting for age and gender ($p = 0.001$), although marginally weaker (β [95% CI] went from

and 88 controls and the ACC/AHA risk score in 152 patients and 98 controls. Neither score demonstrated a significant difference in 10-year CV risk between patients and controls, as presented in Table 3. The proportions with a 10-year CV risk score >10%[35] were similar between patients (NHLBI: 54%, ACC/AHA: 75%) and controls (NHLBI: 44%, ACC/AHA: 64%), NHLBI $p = 0.17$ and ACC/AHA $p = 0.069$.

Table 4. Factors associated with skin AF in patients with COPD.

Dependent variable: Skin AF

	B	95% CI
Diabetes (yes)	0.34	0.27 to 0.60
$FEV_1\%$ predicted (per %)	−0.005	−0.007 to −0.003
Age (per year)	0.015	0.008 to 0.022

CI: confidence interval; AF: autofluorescence; FEV_1: forced expiratory volume in 1 second; COPD: chronic obstructive pulmonary disease.

−0.252 [−0.385, −0.12] to −0.216 [−0.343, −0.086]).In the subgroup without IHD or diabetes, the skin AF remained greater in patients with COPD 3.0(0.5) AU than controls 2.7(0.5) AU, $p = 0.001$ and again remained significant after adjustment for confounders of age and gender, $p = 0.003$.

Skin AF in relation to self-reported IHD and diabetes

There was no significant difference in the skin AF of patients with COPD with and without IHD, $p = 0.18$. There was a significant difference in skin AF between patients with COPD who had diabetes $n = 25$, 3.4 (0.6) AU and those without $n = 160$, 3.0 (0.5) AU; $p = 0.002$.

Variables associated with skin AF

Skin AF was related to chronological age in patients, $r = 0.146$, $p = 0.047$ and controls $r = 0.368$, $p < 0.001$. It was inversely related to $FEV_1\%$ predicted in the COPD group, $r = -0.20$, $p = 0.005$ but not in controls, $r = 0.050$, $p = 0.608$. There was no correlation between skin AF and either eGFR or smoking pack-years in the patients or controls. Skin AF was not significantly different between current and ex-smoker patients.

$FEV_1\%$ predicted, chronological age and co-existent presence of diabetes were the significant predators of skin AF and these variables accounted for 11.6% of the variance of Skin AF, as shown in Table 4.

Aortic stiffness is increased in patients with COPD and associated with Skin AF

Aortic PWV was greater in patients with COPD, 10.2 (2.3) m/s compared to the controls, 9.6 (2.0) m/s,

$p = 0.02$ despite similar MAP (Table 3). In the subset without self-reported IHD and diabetes, aortic PWV remained significantly higher in patients with COPD ($n = 132$) 10.1 (2.2) m/s compared to controls ($n = 88$) 9.3 (1.9) m/s, $p = 0.006$.

In patients, aortic PWV was not related to $FEV_1\%$ predicted but was to age ($r = 0.351$, $p < 0.001$) and MAP ($r = 0.218$, $p = 0.004$).The association with MAP was not altered when adjusted for age and gender.

In the patients, the association between the aortic PWV and skin AF was $r = 0.18$, $p = 0.01$ and was weakened after adjustment for age and gender, $p = 0.06$ (β [95% CI] went from 0.744 [0.147, 1.34] to 0.478 [−0.095, 1.05].

There were 95 (51%) patients and 41 (39%) controls with an aortic PWV >10 m/s, $p = 0.039$. The skin AF was greater in patients with a high aortic PWV: 3.10 (0.55) AU compared to those with a PWV <10 m/s: 2.85 (0.55) AU, $p < 0.001$. This remained significant after adjustment for age and gender, $p = 0.047$.

sRAGE is not different between patients with COPD and controls

The geometric mean (SD) sRAGE was not significantly different between patients with COPD ($n = 182$): 957.8(1.7) pg/mL and controls ($n = 105$): 1057.0 (1.6) pg/mL $p = 0.13$. However, in the subgroup without IHD or diabetes, sRAGE was significantly lower in patients: 891.3 (1.7) pg/mL compared to controls: 1079.2 (1.7) pg/mL $p = 0.01$.

Log_{10} sRAGE was not related to skin AF; $r = -0.08$, $p = 0.25$. In patients there was a significant difference in sRAGE between those with self-reported IHD $n = 33$:1245.9 (1.72) pg/mL and those without $n = 149$:894.5 (1.69) pg/mL $p < 0.01$. However, there was no difference in sRAGE between patients with and without diabetes. There was no association of sRAGE to aortic PWV.

Discussion

Patients with COPD have both a significantly greater skin AF and aortic stiffness than controls with a smoking history. Although there was a greater prevalence of self-reported IHD in patients with COPD compared to the control group, the 10-year future CV risk score calculators did not significantly distinguish between the two subject groups. Taken together, this work

suggests that alternative strategies might need to be employed to best detect future CV risk in COPD.

Skin AF has been shown to be a measure of long-term metabolic burden which has been strongly associated with CV disease and mortality in patients with diabetes,[24] CV risk factors in renal disease,[23] those with a CV history[36] and also subclinical and clinical atherosclerosis independent of diabetes and renal disease.[25] It is a straightforward, quick, non-invasive measurement and this work extends previously published work[22] demonstrating increased skin AF in patients with COPD across a range of moderate to very severe airways obstruction by considering the CV implications of increased skin AF.

Although there was no difference in skin AF between those with and without self-reported IHD, an important consideration is the likely subclinical CV disease in COPD,[37,38] which in itself reinforces the need to consider a new approach to CV prognostication such as skin AF. We did not objectively assess presence of IHD with invasive testing or imaging. Nor did we subcategorize self-reported IHD into a historical acute myocardial infarction or current symptomatic cardiac ischaemia. Contrary to our findings, Mulder et al. showed that skin AF was higher in subjects with stable coronary artery disease compared to controls, however, these subjects had undergone considerable investigations to establish or exclude vascular disease.[36] Further, skin AF was increased in those with subclinical atherosclerosis as well as clinical atherosclerosis, independent of diabetes and renal disease[25] in a study of patients referred to a vascular clinic.

Once again, aortic PWV, a non-invasive independent predictor of CV risk[11,31] in this age group of subjects, was greater in patients with COPD compared to controls, independent of age and gender and in the setting of similar MAP. The difference was seen in an unselected group of patients and controls, and similarly in the subset of patients and controls without self-reported IHD or diabetes mellitus. The clinical implications of increased aortic stiffness is growing for both macrovascular and microvascular disease[39,40] with a 1 m/second increase in aortic PWV relating to a 15% increase in CV mortality and all-cause mortality.[40] Amongst Framingham participants, the addition of aortic PWV predicted first CV events and further, improved the 10-year risk classification when added to the standard risk factors by 13%.[41] Whilst aortic PWV is not in current clinical practice, there have been discussions on its role as a Food and Drug Administration outcome[42] and developments in equipment permit cost-effective, user-friendly options for clinical assessment.

The weak association we reported of skin AF with aortic stiffness does not detract from skin AF as a potential prognostic marker for future CV disease[24,43] particularly given aortic stiffness is a surrogate in itself for a hard end point of CV event or death. A longitudinal study is required. Others have reported an independent association between skin AF and aortic PWV in patients with type 1 diabetes and with brachial-ankle PWV in 120 Japanese patients with end-stage renal failure,[27,44] but this is not universally seen.[45]

Of note, was the lack of difference in the traditional CV risk scores between patient and controls. Current calculators consider smoking categorically as 'current smoker or not' but have no lung disease–related factor or gradation of smoking exposure. Thus a heavy ex-smoker with COPD who stopped a few months back would score less than a control smoker with a 10 pack-year history, provided other variables were the same. Theoretically, the reported increased CV risk in patients with COPD could have been attributed to subtle differences in the other variables, but this does not seem to be the case. For the small difference between the groups in proportion with a CV risk >10%, we lacked power but had the proportions reflected the fold change in future morbidity and mortality previously reported, the study would have been powered. Other disease states such as rheumatoid arthritis have required modification of the risk scores or introduction of novel methods to account for the increased risk in that condition. This raises the question of whether a modified COPD CV calculator is required but also opens consideration of other biomarkers to detect increased CV risk, which could translate into meaningful outcome.

A little unexpectedly given previous literature was that sRAGE levels were not statistically different between patients and controls overall, however, were significantly lower in patients in the subgroup without self-reported IHD and diabetes. Smith et al. previously reported lower sRAGE levels in patients with COPD compared to controls, including patients GOLD II or worse (unlike our study where GOLD I were also included) and their reported levels were generally much lower.[15] Gopal et al. have similarly shown lower sRAGE in patients with COPD and related to lung function.[18,46] In that study, sRAGE was lower in those patients with COPD receiving

long-term oxygen compared to patients who were not.[46] There are also associations of sRAGE to emphysema, something we did not assess.[16,47] Literature on sRAGE in patients with and without CV disease is mixed, though not been studied in patients with COPD in this respect.[48,49] Lastly, genetics may well also be a potential confounder – we did not take into account the presence/absence of the single nucleotide polymorphism in RAGE in our subjects including, for example, rs2070600 (Gly82Ser, C/T) that has been identified as a genetic determinant of serum sRAGE levels,[16,50] shown association with FEV_1[17,51] and COPD.[52]

Limitations

This study group reflects a typical clinical outpatient population in order to be representative. We opted for this approach as hidden comorbid disease exists and excluding a subset with a prior diagnosis is arbitrary. The study is limited by its cross-sectional design and reinforces the need for a longitudinal study with hard endpoints.

Future direction

Prospective, larger, longitudinal studies are needed to fully evaluate the prognostic value that CV indicators may offer in identifying a high-risk group of patients with COPD for future CV disease. This approach parallels a need for a major shift in the care of patients with COPD to address the CV risk in patients with COPD at diagnosis and at assessments. Although further work is required to optimize the ideal CV risk assessment, management of known modifiable risk factors in a systematic approach such as smoking cessation, lipid reduction and optimisation of BP should be considered. Certainly with 30% being current smokers in the patient population, there is opportunity for evidence-based interventions.

Conclusion

Skin AF and aortic stiffness, known independent predictors of future CV events and death in different populations are increased in patients with COPD compared to controls, where, importantly, traditional CV risk scores alone may not sufficiently identify the increased risk. A new approach to address and identify CV risk in patients with COPD is required and a longitudinal study timely.

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