Fibrinogen does not relate to cardiovascular or muscle manifestations in COPD: cross-sectional data from the ERICA study

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ABSTRACT

Cardiovascular and skeletal muscle manifestations constitute important comorbidities in COPD, with systemic inflammation proposed as a common mechanistic link. Fibrinogen has prognostic role in COPD. We aimed to determine whether aortic stiffness and quadriceps weakness are linked in COPD, and whether they are associated with the systemic inflammatory mediator—fibrinogen. Aortic pulse wave velocity (aPWV), quadriceps maximal voluntary contraction (QMVC) force and fibrinogen were measured in 729 patients with stable, Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages II–IV COPD. The cardiovascular and muscular manifestations exist independently ($P=0.22$, χ^2). Fibrinogen was not associated with aPWV or QMVC ($P=0.628$ and $P=0.621$, respectively), making inflammation, as measured by plasma fibrinogen, an unlikely common aetiological factor.

INTRODUCTION

Cardiovascular disease and locomotor muscle dysfunction are two important comorbidities in COPD, occurring in up to 50%^{1,2} of patients, and relating to both increased healthcare utilisation and mortality, thus representing potential therapeutic targets. Both share common risk factors, including smoking, exacerbations and physical inactivity, but systemic inflammation has been also proposed as a mechanistic link between them. If so, novel anti-inflammatory therapies might simultaneously target both manifestations. Fibrinogen is the only inflammatory biomarker with regulatory approval as a drug development tool in COPD, but hitherto the value of fibrinogen in predicting these phenotypes has not been examined.

In the 'Evaluating the Role of Inflammation in Chronic Airways disease' (ERICA) study, we investigated whether cardiovascular and skeletal muscle manifestations overlap in COPD and whether these manifestations are associated with plasma fibrinogen. ERICA is unique among multicentre studies in objectively quantifying these non-pulmonary manifestations of COPD.

METHODS

Methods have been described previously.³ ERICA is a prospective, observational study that recruited

subjects from hospital and community settings, and was registered with the UK Clinical Research Network Study Portfolio (<http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=11101>). Participants provided written consent to participate.

Subjects were aged 40–90 years with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages II–IV COPD judged by postbronchodilator spirometry. Relevant exclusion criteria were alpha-1-antitrypsin deficiency or significant coexisting pulmonary disease; subjects were clinically stable for >4 weeks. Comorbid disease was not an exclusion criterion.

Subjects underwent multiple phenotypic assessments, including aortic pulse wave velocity (aPWV), quadriceps maximal voluntary contraction (QMVC) force, 6 min walk distance (6MWD) and fibrinogen.

aPWV of >10 m/s was chosen as a surrogate measure of cardiovascular disease.⁴ Quadriceps weakness was defined according to the gender-specific Seymour equation.² The 'Cardiovascular' group contained subjects with elevated aPWV alone, 'Muscle' contained subjects with skeletal muscle weakness only, 'Both' contained subjects with both manifestations and 'Neither' had subjects with neither manifestation.

Multiple linear regression analyses were conducted to estimate the dependence of QMVC and aPWV on fibrinogen, with adjustment for known or expected confounders. Non-normally distributed variables were log-transformed prior to analysis.

χ^2 testing was carried out to test whether QMVC and aPWV were independently associated.

Analyses were performed using R V.3.0.0 for Microsoft Windows with RStudio V.0.98.953.

RESULTS

Seven hundred and forty-six people were screened; 729 met the inclusion criteria and 617 subjects had both aPWV and QMVC measurements. Table 1 describes the baseline demographics for the whole cohort and phenotypic groups. The population had a mean age of 67 years, 61% were male, with a mean FEV₁ of 52.2% predicted, mean aPWV of 10.3 m/s and mean QMVC of 30.6 kg (68.2% predicted).

Of 617 subjects, 194 (31.4%) were classified

Table 1 Baseline demographics

Variable	Overall (n=729)	Neither (n=194)	Muscle (n=137)	Cardiovascular (n=154)	Both (n=132)
Age (years)	67 (8)	66 (7)***	63 (8)***	70 (7)***	70 (7)***
Gender (% male)	60.6	58.3	54.7	67.5	62.9
Smoking history (total pack years)	47 (28)	45 (27)	47 (26)	51 (31)	47 (28)
BMI (kg / m ²)	27.3 (5.8)	26.3 (4.9)**	26.9 (5.6)	27.1 (4.9)	28.3 (6.5)*
Fat-free mass (kg)	51.0 (11.1)	49.7 (10.6)	50.1 (11.2)	51.9 (10.5)	52.2 (11.9)
CAT score (0–40)	20 (0–40)	17 (0–38)***	22 (1–39)**	19 (3–40)	21.5 (6–40)*
SGRQ total score	51.4 (22.3)	44.2 (21.2)***	57.4 (21.5)***	47.7 (22.5)*	55.8 (20.5)*
FEV ₁ (L)	1.34 (0.53)	1.50 (0.52)***	1.31 (0.53)	1.32 (0.50)	1.26 (0.50)
FEV ₁ (% predicted)	52.2 (16.1)	57.4 (14.2)***	49.4 (16.3)*	51.8 (16.4)	50.5 (15.8)
FEV ₁ /FVC	0.48 (0.13)	0.49 (0.12)	0.48 (0.13)	0.47 (0.12)	0.49 (0.13)
Muscle indices					
QMVC (kg)	30.6 (11.5)	36.1 (10.1)	23.4 (7.9)	36.7 (10.7)	22.7 (8.2)
QMVC (% predicted)	68.2 (20.7)	81.4 (15.3)	51.5 (12.0)	82.2 (14.9)	50.2 (12.9)
SPPB total score	10 (1–12)	11 (3–12)***	10 (3–12)	11 (4–12)**	9 (2–12)***
6MWD (m)	345 (130)	404 (104)***	338 (129)	361 (125)	282 (132)***
Cardiovascular indices					
Supine MAP (mm Hg)	98 (12)	96 (11)*	95 (10)***	100 (10)*	100 (11)*
aPWV (m/s)	10.3 (2.6)	8.3 (1.1)	8.3 (1.1)	12.2 (2.0)	12.7 (1.9)
Inflammatory markers					
Fibrinogen (g/dL)	3.49 (0.86)	3.44 (0.95)	3.41 (0.76)	3.49 (0.78)	3.52 (0.90)
hsCRP (mg/L)	6.57 (12.1)	7.45 (19.7)	6.11 (8.13)	5.63 (6.95)	6.365 (6.55)
WCC (×10 ⁹ /L)	7.50 (2.16)	7.32 (2.15)	7.19 (2.18)	7.42 (1.95)	7.70 (2.38)
Comorbidities					
Exacerbations per year	1.9 (2.1)	1.71 (1.8)	2.2 (2.0)*	1.81 (2.34)	2.2 (2.3)*
Diabetes (%)	11.4	6.3	7.2	10.4	18.3**
Antihypertensive therapy (%)	35.9	31.4	28.9	39.0	43.9*
Cholesterol-lowering therapy (%)	32.6	22.8	28.5	37.9**	43.8***
Previous myocardial infarction (%)	7.9	6.3	6.6	9.1	9.2

Baseline demographics for overall cohort (n=729) and phenotypic groups. Values expressed as mean (SD) for continuous variables and median (range) for discrete variables. The 'Neither' group (n=194) represents subjects with neither elevated aPWV nor skeletal muscle weakness. The 'Muscle' group (n=137) represents subjects with skeletal muscle weakness alone. The 'Cardiovascular' group (n=154) represents subjects with cardiovascular manifestation, defined as elevated aPWV, alone, and the 'Both' group (n=132) contains subjects demonstrating both skeletal muscle weakness and elevated aPWV. Skeletal muscle weakness according to predicted QMVC based on equations developed by Seymour *et al*² and elevated aPWV defined as >10 m/s.

*P<0.05, **P<0.01, ***P<0.001 for significant differences across groups. For continuous variables, the P value represents differences between overall mean and group mean. For ordinal and binary variables, the P value represents differences between the 'Neither' group and the remaining groups. Adjustments have not been made for multiple comparisons.

6MWD, 6 min walk distance; aPWV, aortic pulse wave velocity; BMI, body mass index; CAT, COPD Assessment Test; hsCRP, high-sensitivity C reactive protein; MAP, mean arterial pressure; QMVC, quadriceps maximal volitional contraction; SGRQ, St George's Respiratory Questionnaire; SPPB, short physical performance battery; WCC, white cell count.

as 'Neither', 137 (22.2%) as 'Muscle', 154 (30.0%) as 'Cardiovascular' and 132 (21.4%) as 'Both' (supplementary eFigure 1). Overall, 269 out of 617 (43.6%) subjects had muscle weakness and 286 out of 617 (46.4%) had elevated aPWV. X² test confirmed that cardiovascular and skeletal muscle manifestations were independent (test statistic 1.49; P = 0.22).

Fibrinogen was not significantly associated with either APWV or QMVC (P = 0.628 and P = 0.621) (figure 1, supplementary eTable 2 and eTable 3).

Age, gender, supine heart rate, supine mean arterial pressure and diabetes were significantly associated with aPWV (online supplementary eTable 2). Smoking history, FEV₁, previous self-reported myocardial infarction, antihypertensive therapy and cholesterol-lowering therapy were not significantly associated.

QMVC was significantly and independently associated with

age, gender, fat-free mass and FEV₁ (online supplementary eTable 3). Smoking history and height were not significant associations.

DISCUSSION

Cardiovascular and skeletal muscle manifestations are more prevalent in COPD than previously reported, but do not coexist more frequently than is expected by chance and therefore likely require different therapeutic approaches. Furthermore, fibrinogen was not associated with quadriceps strength or aortic stiffness, suggesting that it is unlikely to be useful in clinical trials addressing cardiovascular or skeletal muscle manifestations in COPD. Our findings do not support the concept that anti-inflammatory therapy aiming to reduce fibrinogen is

Figure 1 Relationship between fibrinogen and aPWV and QMVC. Scatterplot demonstrating relationship between (A) fibrinogen (g/L) and arterial stiffness, as measured by aPWV (m/s) in 651 subjects with COPD, with Spearman's correlation of 0.05 and $P=0.25$; and (B) fibrinogen (g/L) and quadriceps weakness, as measured by QMVC (kg) in 684 subjects with COPD, with Spearman's correlation -0.10 and $P=0.009$. aPWV, aortic pulse wave velocity; QMVC, quadriceps maximal volitional contraction.

likely to reduce aortic stiffness or improve quadriceps strength in COPD.

Our estimate of cardiovascular comorbidity agrees with previous estimates. Associations with aPWV in our patients were similar to those previously observed in healthy subjects.⁴ Interestingly fibrinogen was not associated with arterial stiffness, despite prior reports of association of aPWV with interleukin-6 and C reactive protein (CRP); moreover, we failed to find associations between white cell count, CRP and aPWV or QMVC (online supplementary eTables 4–13). Furthermore, we did not find an association between FEV_1 and aPWV, in contrast to smaller studies,⁵ suggesting that aPWV is not linked to the severity of airflow limitation in people diagnosed with COPD.

In our cohort, the prevalence of quadriceps weakness (43.6%) is higher than previously reported.² In COPD, muscle weakness precedes the development of whole body cachexia, with relative upper limb sparing⁶; therefore, measures other than QMVC (eg, hand grip strength or bioimpedance) are likely to underestimate the prevalence of muscle dysfunction.

This study is one of the few to have examined the coexistence of cardiac and muscle manifestations. Using different methodologies prior studies found lower prevalences; Vanfleteren *et al*⁷ reported 10% of patients in their cardiovascular cluster had muscle wasting while 7% of patients with cachexia had a history of myocardial infarction. Siebeling *et al*⁸ estimate the coexistence of cardiovascular and muscular comorbidities at 2%–3%. Of our cohort, 21.4% exhibited both elevated aPWV and quadriceps weakness; χ^2 testing confirmed that there is not an independent, overlap syndrome.

Our study supports recent data that refute the link between low-grade systemic inflammation and cardiovascular or muscle manifestations in COPD.^{7–9} Persistent systemic inflammation is present in 16% of patients with COPD¹⁰; given that we report prevalence of both aPWV and QMVC is much higher than 16%, inflammation seems an improbable key aetiological factor. The cross-sectional nature of our data means that a temporal link between PWV and QMVC or systemic inflammation cannot be assessed at this stage, although follow-up of the cohort is ongoing. Additionally, it is important to note that our study allowed the cross-sectional assessments to be carried out over either a single visit or two visits within a 3-month period; therefore, we acknowledge that in some patients inflammatory markers were measured on a separate day to aPWV and QMVC. A further limitation is that 112 patients of the entire data set did not have the three key measures assessed here. These patients were similar in most respects to the cohort analysed here but had a lower FEV_1 and 6MWD (data not shown).

In conclusion, cardiovascular and skeletal muscle manifestations are prevalent in COPD, with muscle weakness being more common than previously thought. These extrapulmonary manifestations are distinct and need to be addressed individually. Neither aortic stiffness nor quadriceps weakness relates to plasma fibrinogen, suggesting that this is not a useful biomarker for trials addressing these manifestations and that inflammation is an unlikely aetiological factor.

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Patient consent Obtained.

Ethics approval The Cambridge South Research Ethics Committee (reference 11/EE/0357) approved the study.

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