Fibrinogen does not relate to cardiovascular or muscle manifestations in chronic obstructive pulmonary disease (COPD): cross-sectional data from the ERICA study

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Author's contributions

MIP, DM, JRF, CMM, CEB, JRC, WM, JF, NSG, MF, JC, DAL, PAMC, BEM, RT-S and IBW all made substantial contributions to the conception and design of the work. MIP, DM, JRF, MA, CMM, CEB, JRC, WM, JF, MM, SN, NSG, MF, and IBW made substantial contributions to the acquisition and analysis of data for the work. All authors contributed to the interpretation of the data, drafting and revision of the manuscript and final approval of the version submitted for publication. All authors take accountability for all aspects of the work.

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This article has an online data supplement.

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 volitional contraction force (QMVC) and fibrinogen were measured in 729, stable, GOLD stage II-IV COPD patients.

The cardiovascular and muscular manifestations exist independently (p=0.22, Chi squared). 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 utilization 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). Cambridge South Research Ethics Committee (reference 11/EE/0357) approved the study, and participants provided written consent to participate.

Subjects were aged 40-90 years with GOLD stage II-IV COPD judged by post-bronchodilator spirometry. Relevant exclusion criteria were alpha-1-antitrypsin deficiency or significant co-existing 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 volitional contraction force (QMVC), 6-minute walk distance (6MWD) and fibrinogen.

APWV of >10m/s was chosen as a surrogate measure of cardiovascular disease [4]. Quadriceps weakness was defined according to the gender-specific Seymour equation [2]. Group 'Cardiovascular' 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.

Chi-square testing was carried out to test whether QMVC and aPWV were independently associated.

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

Results

746 people were screened; 729 met inclusion criteria and 617 subjects had both aPWV and QMVC measurements. Table 1 describes baseline demographics for the whole cohort and phenotypic groups. The population had a mean age of 67 years, 61% were males, with mean FEV_1 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 as 'Neither', 137 (22.2%) as "Muscle", 154 (30.0%) as "Cardiovascular" and 132 (21.4%) as "Both" (Figure 1). Overall, 269 out of 617 (43.6%) subjects had muscle weakness and 286 out of 617 (46.4%) had elevated aPWV. Chi-square test confirmed that cardiovascular and skeletal muscle manifestations were independent (test statistic 1.49; p=0.22).

Age, gender, supine heart rate, supine mean arterial pressure and diabetes were significantly associated with aPWV (eTable 2). Smoking history, FEV_1, previous self-reported myocardial infarction, anti-hypertensive therapy and cholesterol lowering therapy were not significantly associated.

QMVC was significantly and independently associated with age, gender, fat-free mass and FEV_1 (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 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 CRP; moreover we failed to find associations between WCC, CRP and aPWV or QMVC (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 sparing [6], therefore measures other than QMVC (for example handgrip strength or bioimpedence) are likely to underestimate the prevalence of muscle dysfunction.

This study is one of the few to have examined the co-existence of cardiac and muscle manifestations. Using different methodologies prior studies found lower prevalences;

Vanfleteren [7] reported 10% of patients in their cardiovascular cluster had muscle wasting while 7% of cachectic patients had a history of myocardial infarction. Siebeling *et al* [8] estimate co-existence of cardiovascular and muscular comorbidities at 2-3%. 21.4% of our cohort exhibited both elevated aPWV and quadriceps weakness; chi-squared testing confirmed that there is not an independent, overlap syndrome.

Our study supports recent data that refutes 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 COPD [10]; 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 three 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 3 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 commoner than previously thought. These extra-pulmonary manifestations are distinct, and need to be addressed individually. Neither aortic stiffness nor quadriceps weakness relate 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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Declaration of Interests

MIP has received payment to his institution or himself for advice on skeletal muscle weakness in COPD from GSK, Novartis, AZ, Pfizer, Lilly and Astellas. DM is an employee and shareholder of GSK. JRF, CMM, MM, SN and NG have no conflict of interest to report. CEB reports grants from Innovate UK (formerly Technology Strategy Board (TSB) UK) during the conduct of the study; advisory board fees from GSK paid to their institution, grants from GSK, grants from MRC/ABPI outside the submitted work. JRC reports grants from TSB/MRC, during the conduct of the study; personal fees from GSK, outside the submitted work. WM received research support from GlaxoSmithKline and Pfizer, and was on advisory committees of Almirall, GlaxoSmithKline, Novartis, and Pfizer; he was a speaker for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Janssen, and Novartis. JF received speaker fees from GSK. MF acknowledges receipt of an imaging fellowship award from GSK. JC is employed full-time by Cambridge University Hospitals National Health Service

Foundation Trust and is obligated to spend 50% of his time on GSK clinical trial research, representing a significant relationship; however, he receives no other benefits or compensations from GSK. DAL reports grants and personal fees from GSK, personal fees from Grifols, outside the submitted work. PMAC has advised Boehringer Ingelheim, GSK, AstraZeneca and Takeda on the design and conduct of clinical trials and has spoken at meetings sponsored by these companies and by Novartis; he has no stock holdings in any pharmaceutical company or connection with the tobacco industry. BEM and RT-S are share-holders and employees of GSK. IBW reports grants from TSB, and GSK during the conduct of the study and grants from GSK, outside the submitted work.

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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) ***
6 MW distance (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 (x10^9/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**
Anti-hypertensive 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

Table 1: Baseline demographics for overall cohort (n = 729) and phenotypic groups. Values expressed as mean (standard deviation) for continuous variables and median (range) for discrete variables. Group 'Neither' (n=194) represents subjects with neither elevated aortic pulse wave velocity nor skeletal muscle weakness. Group 'Muscle' (n=137) represents subjects with skeletal muscle weakness alone. Group 'Cardiovascular' (n=154) represents subjects with cardiovascular manifestation, defined as elevated aortic pulse wave velocity, alone, and group 'Both' (n=132) contains subjects demonstrating both skeletal muscle weakness and elevated aortic pulse wave velocity. Skeletal muscle weakness according to predicted quadriceps maximal volitional contraction, based on equations developed by Seymour et al [2] and elevated aortic pulse wave velocity defined as >10 m/s.

* p-value <0.05, ** p-value <0.01 and *** p-value of <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, p-value represents differences between group 'Neither' and the remaining groups. Adjustments have not been made for multiple comparisons.

List of abbreviations: BMI = body mass index, FEV_1 = forced expiratory volume in 1 second, QMVC = quadriceps maximal volitional contraction, SPPB = short physical performance battery, 6MW = 6 minute walk, MAP = mean arterial pressure, aPWV = aortic pulse wave velocity, CRP = C-reactive protein, WCC = white cell count, CAT = COPD assessment test, SGRQ = St George's respiratory questionnaire

Figure 1 Relationship between fibrinogen and APWV and QMVC

Figure 1: Scatterplot demonstrating relationship between: (a) fibrinogen (g/L) and arterial stiffness, as measured by aortic pulse wave velocity (PWV) (m/s) in 651 subjects with COPD, with Spearman correlation of 0.05, p = 0.25; and (b) fibrinogen (g/L) and quadriceps weakness, as measured by quadriceps volitional contraction (QMVC) (kg) in 684 subjects with COPD, with Spearman correlation -0.10 and p=0.009.