



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Associations between COPD related manifestations

Citation for published version:

Romme, EA, McAllister, DA, Murchison, JT, Van Beek, EJ, Petrides, GS, Price, CO, Rutten, EP, Smeenk, FW, Wouters, EF & MacNee, W 2013, 'Associations between COPD related manifestations: a cross-sectional study' *Respiratory research*, vol. 14, no. 1, 129. DOI: 10.1186/1465-9921-14-129

Digital Object Identifier (DOI):

[10.1186/1465-9921-14-129](https://doi.org/10.1186/1465-9921-14-129)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Publisher's PDF, also known as Version of record

Published In:

Respiratory research

Publisher Rights Statement:

© 2013 Romme et al.; licensee BioMed Central Ltd.

This is an open access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



RESEARCH

Open Access

Associations between COPD related manifestations: a cross-sectional study

Elisabeth APM Romme^{1,2*}, David A McAllister³, John T Murchison⁴, Edwin JR Van Beek⁵, George S Petrides⁶, Cameron OS Price⁴, Erica PA Rutten⁷, Frank WJM Smeenk¹, Emiel FM Wouters² and William MacNee⁸

Abstract

Background: Cardiovascular disease, osteoporosis and emphysema are associated with COPD. Associations between these factors and whether they predict all-cause mortality in COPD patients are not well understood. Therefore, we examined associations between markers of cardiovascular disease (coronary artery calcification [CAC], thoracic aortic calcification [TAC] and arterial stiffness), bone density (bone attenuation of the thoracic vertebrae), emphysema (PI-950 and 15th percentile) and all-cause mortality in a COPD cohort.

Methods: We assessed CAC, TAC, bone attenuation of the thoracic vertebrae, PI-950 and 15th percentile on low-dose chest computed tomography in COPD subjects. We measured arterial stiffness as carotid-radial pulse wave velocity (PWV), and identified deaths from the national register.

Results: We studied 119 COPD subjects; aged 67.8 ± 7.3 , 66% were males and mean FEV₁% predicted was 46.0 ± 17.5 . Subjects were classified into three pre-specified groups: CAC = 0 (n = 14), $0 < \text{CAC} \leq 400$ (n = 41) and CAC > 400 (n = 64). Subjects with higher CAC were more likely to be older ($p < 0.001$) and male ($p = 0.03$), and more likely to have higher systolic blood pressure ($p = 0.001$) and a history of hypertension ($p = 0.002$) or ischemic heart disease ($p = 0.003$). Higher CAC was associated with higher PWV (OR 1.62, $p = 0.04$) and lower bone attenuation (OR 0.32, $p = 0.02$), but not with 15th percentile, after adjustment for age, sex and pack-years of smoking. In a Cox proportional hazards model, CAC, TAC and 15th percentile predicted all-cause mortality (HR 2.01, 2.09 and 0.66, respectively).

Conclusions: Increased CAC was associated with increased arterial stiffness and lower bone density in a COPD cohort. In addition, CAC, TAC and extent of emphysema predicted all-cause mortality.

Trial registration: Lothian NHS Board, Lothian Research Ethics Committee, LREC/2003/8/28.

Keywords: Arterial calcification, Arterial stiffness, Bone density, Cardiovascular disease, Co-morbidity, Computed tomography, COPD, Emphysema, Mortality, Osteoporosis

Background

Chronic obstructive pulmonary disease (COPD), in addition to its pulmonary manifestations, is associated with significant extrapulmonary manifestations. Cardiovascular disease and osteoporosis are recognised extrapulmonary manifestations, whose prevalence is higher in COPD patients than in control subjects matched for age and sex [1,2].

In general population studies, a relationship has been suggested between cardiovascular disease and osteoporosis. Postmenopausal women with osteoporosis had a 3.9-fold increased risk of cardiovascular events compared with postmenopausal women with osteopenia [3]. In 2348 postmenopausal women, increased aortic calcification, a marker of cardiovascular disease, was associated with lower bone density and an increased number of vertebral and hip fractures [4], and in a subpopulation studied longitudinally, progression of aortic calcification was associated with bone loss [4].

Although cardiovascular disease and osteoporosis are common in COPD patients [1,2], there are few studies

* Correspondence: lisette.romme@catharinaziekenhuis.nl

¹Department of Respiratory Medicine, Catharina Hospital, Eindhoven, The Netherlands

²Department of Respiratory Medicine, Maastricht University Medical Centre + (MUMC+), P.O. Box 5800, Maastricht 6202 AZ, The Netherlands
Full list of author information is available at the end of the article

on the relationship between cardiovascular disease and osteoporosis in COPD. Sabit and colleagues [5] found that COPD subjects with osteoporosis had increased arterial stiffness, another marker of cardiovascular disease, compared with COPD subjects without osteoporosis. In addition, arterial stiffness and osteoporosis have been shown to relate to the extent of emphysema [6,7]. These data suggest associations between cardiovascular disease, osteoporosis and emphysema. Furthermore, COPD related extrapulmonary manifestations are thought to contribute to morbidity and mortality [8].

The objectives of this study were: 1. To determine the associations between markers of cardiovascular disease (coronary artery calcium [CAC], thoracic aortic calcium [TAC] and arterial stiffness), bone attenuation of the thoracic vertebrae, and extent of emphysema, and 2. To identify whether these factors predict all-cause mortality in a COPD cohort.

Methods

Our analysis was based on the data of a cohort study designed to identify prognostic markers in COPD [6]. The study was conducted in accordance with the amended Declaration of Helsinki, the protocol was approved by the Lothian Research Ethics Committee (LREC/2003/8/28), and all subjects gave written informed consent.

Subjects

The inclusion and exclusion criteria have been described previously [6]. In summary, all subjects were included between April 2003 and December 2005, had a clinical history compatible with COPD, a history of smoking for at least 10 pack-years and evidence of chronic airflow limitation on spirometry. All subjects who had low-dose computed tomography (CT) of the chest were included in our analysis.

Height, weight and post-bronchodilator spirometry were measured according to American Thoracic Society/European Respiratory Society standards. The subjects' self-reported respiratory symptoms, medications, smoking history, occupational exposure, and coexisting medical conditions were documented at study entry using structured interviews.

Arterial stiffness

Peripheral blood pressure was measured in all subjects, and arterial stiffness was assessed in 104 subjects. Arterial stiffness was measured as carotid-radial pulse wave velocity (PWV) as described previously [6]. Briefly, we used the Q-wave of a simultaneously recorded electrocardiograph to identify the onset of the pressure wave, and used applanation tonometry of the carotid and radial arteries to record the pressure waveform at the

peripheral site. The difference in wave transit time between the carotid and radial arteries was used to calculate carotid-radial PWV.

CT scanning

Low-dose CT scanning of the chest was performed without contrast media at full inspiration using a 16-slice multi-detector-row CT scanner (135 kV, 20 mAS; Toshiba Aquilion, Toshiba, Japan). Images were reconstructed with a slice thickness of 1 mm increment using an FC-03 filter (Toshiba, Japan).

CAC and TAC were assessed on the standard images used for analysis of the lungs as previously described [9]. Images were analysed on a dedicated post-processing workstation (VOXAR 3D) using calcium analysis software. CAC and TAC were quantified using the Agatston score [10]. Calcification was defined as an area ≥ 1 mm² in the axial plane of a coronary artery or the thoracic aorta with an attenuation threshold of ≥ 130 Hounsfield units. Regions of interest were drawn, and CAC and TAC were calculated by multiplying by a weighting factor selected dependent on the peak signal within the region of interest. Total CAC was obtained by summing the weighted scores from each coronary artery, and total TAC was obtained by summing the weighted scores from the ascending aorta, aortic arch and descending aorta superiorly to the upper limit of the thoracic vertebrae 12 (T12). The CT images of a random sample of 25 patients were independently assessed by two observers and assessed by one observer twice. The intra-class correlation coefficients were high for inter-observer and intra-observer agreements for CAC (0.88 and 0.99 respectively) and TAC (both 0.99).

Emphysema was quantified by in-house software using the 15th percentile point of the frequency distribution of lung attenuation, and pixel index for -950 (PI-950) Hounsfield units as previously described [6]. Bone attenuation of the thoracic vertebrae was measured according to a method described in detail previously [11]. The mean bone attenuation of thoracic vertebrae 4, 7 and 10 (T4, T7 and T10) were determined by placing circular regions of interest in the central parts of the vertebral bodies. The average bone attenuation of these three vertebrae T4, T7 and T10 was calculated and expressed in Hounsfield units.

Mortality

Deaths occurring anywhere in the United Kingdom were identified by obtaining records from the General Registry Office for Scotland. Survival time was calculated in number of days from date of CT scan until date of death with a census cut-off date of 31 December 2011.

Statistical analysis

CAC and TAC were log transformed (normalising/linearising transformations). For CAC, subjects were classified into three pre-specified groups: CAC = 0, 0 < CAC ≤ 400 and CAC > 400. Comparisons among the three groups were made using one way analysis of variance (ANOVA) or Kruskal-Wallis test. Univariate and multinomial logistic regression analyses were performed to estimate associations between CAC, TAC, PWV, bone attenuation and 15th percentile. Time to death was compared using Kaplan Meier curves, and Cox proportional-hazards analysis was used to estimate associations between all-cause mortality and CAC, TAC, PWV, bone attenuation and 15th percentile.

All statistical analyses were performed in SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Two-sided p-values ≤ 0.05 were considered statistically significant.

Results

One hundred nineteen COPD subjects (aged 67.8 ± 7.3, 66% were males, mean forced expiratory volume in 1 second [FEV₁]% predicted was 46.0 ± 17.5) were included in our analysis. Subjects with higher CAC were more likely to be older (p < 0.001), male (p = 0.03), and to

have higher systolic blood pressure (p = 0.001), a history of hypertension (p = 0.002) or ischemic heart disease (p = 0.003), higher TAC (p < 0.001) and lower bone attenuation (p = 0.006) (Table 1). As expected there was a significant correlation between CAC and TAC (Spearman's r = 0.57, p < 0.001). Higher CAC was associated with higher PWV (OR 1.62, p = 0.04) and lower bone attenuation (OR 0.32, p = 0.02), but was not associated with FEV₁, 15th percentile and PI-950 after adjustment for age, sex and pack-years of smoking (Table 2). As described previously, PWV correlated with 15th percentile and PI-950 (r = 0.47, p < 0.001) [6]. Bone attenuation was not associated with PWV, 15th percentile or PI-950.

Mortality

The median follow-up was 65 (0–83) months. During the observation period, 30 subjects (25%) died. A respiratory cause of death was the primary aetiology in 18 subjects (60%), and cardiovascular cause of death was the primary aetiology in 7 subjects (23%). In a Cox proportional-hazards model, CAC predicted all-cause mortality after adjustment for age, sex, FEV₁ and pack-years of smoking (HR 2.01, 95% CI 1.13–3.58, p = 0.02, Table 3). Figure 1 and Table 4 show the Kaplan-Meier

Table 1 Clinical characteristics of the total cohort and after stratification for CAC

	Total cohort	CAC = 0	0 < CAC ≤ 400	CAC > 400	p-value
Number of subjects	119	14	41	64	
Age, yrs	67.8 ± 7.3	58.6 ± 6.3	66.1 ± 6.2	70.8 ± 6.2	<0.001
Male, n (%)	79 (66)	7 (50)	24 (59)	48 (75)	0.03
FEV ₁ , % predicted	46.0 ± 17.5	44.2 ± 13.7	43.8 ± 17.4	47.9 ± 18.3	0.47
FVC, % predicted	74.4 ± 20.6	72.6 ± 14.2	74.4 ± 21.0	74.8 ± 21.7	0.94
FEV ₁ /FVC ratio	47.1 ± 12.3	46.9 ± 10.7	44.9 ± 13.5	48.6 ± 11.9	0.33
BMI, kg/m ²	25.8 ± 5.5	25.6 ± 5.9	25.7 ± 5.2	25.9 ± 5.6	0.98
Distance walked, m	369.1 ± 112.2	406.6 ± 105.2	385.9 ± 105.0	349.8 ± 116.1	0.16
Pack-years of smoking, n	45.4 ± 20.5	44.4 ± 20.2	44.6 ± 21.7	46.2 ± 20.0	0.91
Heart rate, beats/min	74.0 ± 13.0	71.5 ± 10.1	73.4 ± 12.0	74.9 ± 14.2	0.65
Blood pressure systolic, mmHg	142.2 ± 23.9	127.7 ± 16.5	136.2 ± 20.3	149.2 ± 25.0	0.001
Blood pressure diastolic, mmHg	79.9 ± 11.3	76.6 ± 11.5	78.0 ± 9.2	81.9 ± 12.1	0.11
Hypertension, n (%)	30 (25)	0 (0)	7 (17)	23 (36)	0.002
Ischemic heart disease, n (%)	22 (19)	0 (0)	4 (10)	18 (28)	0.003
Diabetes, n (%)	7 (6)	0 (0)	2 (5)	5 (8)	0.25
TAC, median (min-max)	1540 (0–20828)	262 (0–4237)	1125 (3–8606)	3475 (0–20828)	<0.001
PWV, m/s	8.90 ± 1.63	8.35 ± 1.36	9.18 ± 1.54	8.86 ± 1.72	0.31
PI-950, median in % (min-max)	6.89 (0.12–43.2)	17.1 (0.12–39.0)	5.32 (0.12–43.2)	6.86 (0.27–38.6)	0.81
15th percentile, HU	−921.9 ± 27.8	−919.9 ± 38.3	−924.2 ± 29.7	−920.8 ± 24.1	0.82
Bone attenuation, HU	138.1 ± 35.5	162.2 ± 37.6	141.8 ± 31.9	130.4 ± 35.0	0.006

Results are presented as mean ± standard deviation unless otherwise indicated.

PWV was assessed in 104 subjects.

BMI body mass index, CAC coronary artery calcium, FEV₁ forced expiratory volume in 1 second, FVC forced vital capacity, HU hounsfield unit, PI pixel index, PWV pulse wave velocity, TAC thoracic aortic calcium.

Table 2 Multinomial regression for CAC

	0 < CAC ≤ 400		CAC > 400		p-value
	Odds ratio	95% CI	Odds ratio	95% CI	
PWV ^a	1.92	1.08 – 3.44	1.62	0.91 – 2.91	0.05
PWV ^b	2.03	1.10 – 3.74	1.62	0.87 – 3.02	0.04
Bone attenuation/SD ^a	0.46	0.21 – 1.03	0.33	0.14 – 0.77	0.02
Bone attenuation/SD ^b	0.43	0.19 – 1.00	0.32	0.13 – 0.76	0.02
FEV ₁ ^a	0.82	0.22 – 3.09	0.84	0.21 – 3.29	0.96
FEV ₁ ^b	0.80	0.21 – 3.05	0.82	0.21 – 3.25	0.95
15th percentile/SD ^a	0.80	0.45 – 1.45	0.64	0.45 – 1.63	0.76
15th percentile/SD ^b	0.80	0.43 – 1.48	0.84	0.43 – 1.64	0.77

Reference category CAC = 0.

^aAfter adjustment for age and sex.

^bAfter adjustment for age, sex and pack-years of smoking.

CI confidence interval, FEV₁ forced expiratory volume in 1 second, PWV pulse wave velocity, SD standard deviation.

curves and numbers at risk. TAC predicted all-cause mortality similarly to CAC (Additional file 1). Lower 15th percentile (more emphysema) was associated with increased all-cause mortality after adjustment for age and sex (HR 0.65, CI 0.45-0.95, p = 0.03), but not after adjustment for age, sex, FEV₁ and pack-years of smoking (p = 0.06) (Additional file 2). PWV and bone attenuation were not associated with all-cause mortality (Additional file 2).

Discussion

We found that increased CAC was associated with increased arterial stiffness and lower bone attenuation in COPD subjects, but was not associated with extent of emphysema. CAC, TAC and extent of emphysema predicted all-cause mortality in our COPD cohort, while arterial stiffness and bone attenuation were not associated with all-cause mortality.

In line with previous studies [4,5], our data suggest a relationship between cardiovascular disease and osteoporosis in COPD patients. In our study, the association between CAC and bone attenuation was independent of age, sex and pack-years of smoking. In a prospective study in 2442 postmenopausal women, the association

between osteoporosis and cardiovascular events was independent of traditional cardiovascular risk factors such as age, cigarette smoking, hypertension and hyperlipidemia [3]. These data suggest that, in addition to common risk factors, other factors might be involved in the vascular-bone relationship, including systemic inflammation [5], disturbance of the receptor activator of NF-κB/receptor activator of NF-κB ligand/osteoprotegerin system or reduced bone perfusion due to generalised atherosclerosis.

Our data showed a weak association between CAC and arterial stiffness in a COPD cohort after adjustment for age, sex and pack-years of smoking. Previous studies in older populations have found associations between CAC and arterial stiffness after adjustment for confounders [12]. Thus, in addition to common risk factors, atherosclerosis may cause arterial stiffening [13], while increased arterial stiffness in turn may promote atherosclerotic changes due to greater shear and intraluminal stresses [14].

In line with previous research [15,16], CAC was not associated with the degree of airflow obstruction or the extent of emphysema. CAC was not associated with the severity of airflow obstruction or the extent of

Table 3 Cox proportional-hazards for all-cause mortality

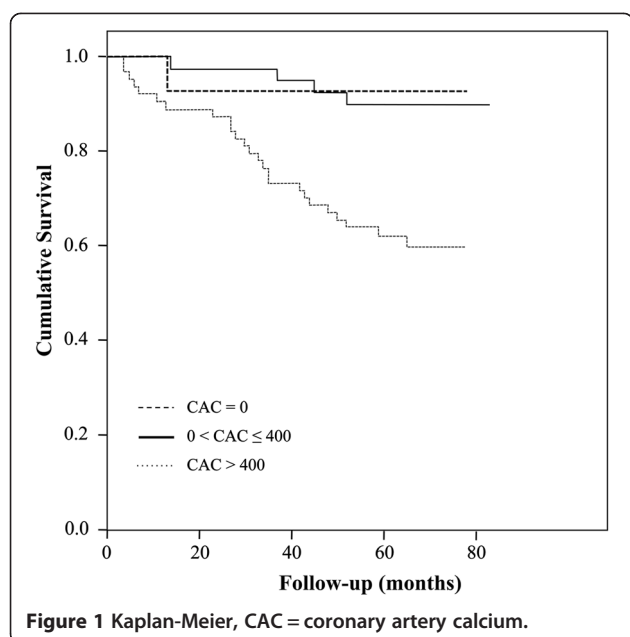
	CAC = 0	0 < CAC ≤ 400	CAC > 400	Per 10-fold increase in CAC	p-value
Number of subjects	14	41	64	-	-
Mortality, n (%)	1 (7)	4 (10)	25 (39)	-	-
CAC	-	1.33	6.46	2.17 (1.29 – 3.65)	0.004
CAC ^a	-	1.18	5.15	2.02 (1.13 – 3.59)	0.02
CAC ^b	-	1.14	5.09	1.94 (1.11 – 3.41)	0.02
CAC ^c	-	1.11	4.98	2.01 (1.13 – 3.58)	0.02

^aAfter adjustment for age and sex.

^bAfter adjustment for age, sex and FEV₁.

^cAfter adjustment for age, sex, FEV₁ and pack-years of smoking.

CAC coronary artery calcium, FEV₁ forced expiratory volume in 1 second.



emphysema in 1159 smokers of the Multicentre Italian Lung Detection (MILD) study [16], and CAC and proximal aortic calcification were not associated with the severity of airflow obstruction in subjects without clinical cardiovascular disease of the Multi-Ethnic Study of Atherosclerosis (MESA) study [15,17]. Notably, as reported previously in this cohort, arterial stiffness did correlate with the extent of emphysema in COPD subjects [6]. The relationship between arterial stiffness and emphysema might be due to connective tissue degradation [6] or elastin degradation [18].

Bone attenuation was not associated with the extent of emphysema. In contrast, a recent review stated that more severe emphysema is associated with reduced bone mineral density [19]. Bon and colleagues [7] showed that the extent of emphysema was independently associated with bone mineral density in 190 current and former smokers, and Ohara and colleagues [20] demonstrated that the extent of emphysema was independently associated with CT measured bone density of the thoracic and lumbar vertebrae in 65 male COPD subjects. The discrepancy between our data and their data might be due to differences in the study population (e.g. smokers versus COPD patients) and methods used (e.g. attenuation threshold of low attenuation areas).

Table 4 Numbers at risk

	CAC = 0	0 < CAC ≤ 400	CAC > 400
0 months	14	41	64
30 months	13	40	52
60 months	10	31	32

CAC coronary artery calcium.

CAC and TAC predicted all-cause mortality after adjustment for age, sex, FEV₁ and pack-years of smoking. Several studies have shown that CAC is a predictor of cardiovascular events and mortality in smokers [21,22]. Here we show that CAC was a strong predictor of all-cause mortality in a COPD cohort. The hazard ratios reported in our COPD subjects were comparable with those reported in smokers and subjects without known coronary artery diseases. In 1159 smokers, the hazard ratio of CAC > 400 was 4.00 (CI 1.17-13.7) for all-cause mortality compared with CAC ≤ 400 after adjustment for age, sex, body mass index and history of diabetes or hypertension [16]. In our study, the hazard ratio of CAC > 400 was 4.6 (CI 1.63-13.12, p = 0.004) compared with CAC ≤ 400 after adjustment for age, sex, FEV₁ and pack-years of smoking. In 3966 subjects without known coronary artery diseases, the crude hazard ratio of CAC ≥ 400 was HR 6.54 (CI 3.51-12.21) for all-cause mortality [23], and in our study the crude hazard ratio of CAC > 400 was 6.46.

Although CAC and TAC were associated with all-cause mortality, arterial stiffness was not associated with all-cause mortality in our COPD cohort. This finding is in contrast to previous studies that have demonstrated a relationship between increased arterial stiffness and all-cause mortality in subjects with chronic kidney disease [24,25]. The lack of a relationship between increased arterial stiffness and mortality in our study might be explained by the fact that we measured carotid-radial PWV rather than carotid-femoral PWV which is the gold standard [26]. A study in 305 end-stage renal disease patients showed indeed that carotid-femoral PWV was an independent predictor of cardiovascular mortality, whereas carotid-radial and femoral-posterior tibial PWV were not associated with mortality [27].

In addition, the extent of emphysema was associated with all-cause mortality after adjustment for age and sex, but not after adjustment for age, sex and FEV₁. As such, it may be that emphysema causes increased mortality indirectly through reducing lung function. Our findings are in line with previous studies that have shown associations between the extent of emphysema and all-cause mortality in COPD subjects [28].

Although lower bone attenuation was associated with increased CAC, bone attenuation was not associated with all-cause mortality in our COPD cohort. In contrast, previous studies have shown that bone density and rate of bone loss are related to mortality in elderly men and women [29,30]. The Rotterdam Study demonstrated that in elderly men the risk of mortality increased when bone density was below average, and that the relationship between bone density and mortality was nonlinear [29]. In addition, Szulc and colleagues [30] showed in 781 elderly men that bone resorption markers predicted

mortality more strongly than bone mineral density. The lack of a relationship between bone attenuation and mortality in our study might be due to the study population (e.g. COPD subjects rather than elderly subjects) and the methods used (e.g. bone attenuation of the thoracic vertebrae rather than bone mineral density of the hip, lumbar spine or whole body).

Our study has several limitations. First, bone attenuation was assessed on low-dose chest CT while dual energy X-ray absorptiometry is the gold standard. However, previous data have demonstrated that bone attenuation measured on CT is strongly correlated with bone mineral density assessed on dual energy X-ray absorptiometry [11]. Second, CAC and TAC were measured on non-gated scans, however, it has been shown previously that measurements of CAC and TAC on non-gated chest CT scans show good agreement with measurements from electrocardiographically gated chest CT scans [9]. Third, arterial stiffness was measured as carotid-radial PWV rather than carotid-femoral PWV which is the gold standard [26]. Although our study has several limitations, we measured several COPD related manifestations such as CAC, TAC, bone attenuation and extent of emphysema in a well-characterised COPD cohort.

Our data showed that CAC, TAC and emphysema which were measured on low-dose chest CT predicted all-cause mortality in COPD subjects. We suggest that low-dose chest CT might contribute to early diagnosis of COPD related manifestations and improved risk stratification, although further evidence, ideally from randomised controlled trials, are required to determine the benefits of this screening approach in COPD patients.

Conclusions

Our study showed that increased CAC was associated with increased arterial stiffness and lower bone attenuation in COPD subjects. CAC, TAC and emphysema predicted all-cause mortality in our COPD cohort, suggesting that quantitative assessment of CAC, TAC and emphysema on chest CT provides relevant prognostic information in COPD subjects.

Additional files

Additional file 1: Cox proportional-hazards for all-cause mortality.

Additional file 2: Cox proportional-hazards for all-cause mortality.

Abbreviations

BMI: Body mass index; CAC: Coronary artery calcification; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; CT: Computed tomography; DEXA: Dual energy x-ray absorptiometry; FEV₁: Forced expiratory volume in 1 second; FVC: Forced vital capacity; HR: Hazard ratio; HU: Hounsfield unit; OR: Odds ratio; PI: Pixel index; PWV: Pulse wave velocity; SD: Standard deviation; TAC: Thoracic aortic calcification.

Competing interest

Elisabeth A.P.M. Romme was the recipient of a European Respiratory Society Fellowship (STRTF 381–2011).

Authors' contributions

EAR contributed to the study idea and design, analysis and interpretation of the results and drafting of the manuscript. DM contributed to the study idea and design, analysis and interpretation of the results, and drafting of the manuscript. JM contributed to the study idea and design, analysis and interpretation of the results, and revision of the manuscript. EvB contributed to the analysis and interpretation of the results, and revision of the manuscript. CP contributed to the analysis and interpretation of the results, and revision of the manuscript. EPR contributed to the analysis and interpretation of the results, and revision of the manuscript. FS contributed to the analysis and interpretation of the results, and revision of the manuscript. EW contributed to the analysis and interpretation of the results, and revision of the manuscript. WM contributed to the study idea and design, analysis and interpretation of the results, and revision of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to thank the respiratory research nurses, Andrew Deans and Joyce Barr, for recruiting COPD subjects.

Author details

¹Department of Respiratory Medicine, Catharina Hospital, Eindhoven, The Netherlands. ²Department of Respiratory Medicine, Maastricht University Medical Centre + (MUMC+), P.O. Box 5800, Maastricht 6202 AZ, The Netherlands. ³Centre for Population Health Sciences, University of Edinburgh, Edinburgh, Scotland, UK. ⁴Department of Radiology, Royal Infirmary of Edinburgh, Edinburgh, Scotland, UK. ⁵Clinical Research Imaging Centre, University of Edinburgh, Edinburgh, Scotland, UK. ⁶Department of Radiology, Freeman Hospital, Newcastle, UK. ⁷Program Development Centre, Centre of expertise for chronic organ failure + (CIRO+), Horn, The Netherlands. ⁸Centre for Inflammation Research, University of Edinburgh, Edinburgh, Scotland, UK.

Received: 21 August 2013 Accepted: 22 October 2013

Published: 19 November 2013

References

1. Graat-Verboom L, Wouters EF, Smeenk FW, Van den Borne BE, Lunde R, Spruit MA: **Current status of research on osteoporosis in COPD: a systematic review.** *Eur Respir J* 2009, **34**:209–218.
2. Mannino DM, Thorn D, Swensen A, Holguin F: **Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD.** *Eur Respir J* 2008, **32**:962–969.
3. Tanko LB, Christiansen C, Cox DA, Geiger MJ, McNabb MA, Cummings SR: **Relationship between osteoporosis and cardiovascular disease in postmenopausal women.** *J Bone Miner Res* 2005, **20**:1912–1920.
4. Schulz E, Arfai K, Liu X, Sayre J, Gilsanz V: **Aortic calcification and the risk of osteoporosis and fractures.** *J Clin Endocrinol Metab* 2004, **89**:4246–4253.
5. Sabit R, Bolton CE, Edwards PH, Pettit RJ, Evans WD, McEnery CM, Wilkinson IB, Cockcroft JR, Shale DJ: **Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease.** *Am J Respir Crit Care Med* 2007, **175**:1259–1265.
6. McAllister DA, Maclay JD, Mills NL, Mair G, Miller J, Anderson D, Newby DE, Murchison JT, MacNee W: **Arterial stiffness is independently associated with emphysema severity in patients with chronic obstructive pulmonary disease.** *Am J Respir Crit Care Med* 2007, **176**:1208–1214.
7. Bon J, Fuhrman CR, Weissfeld JL, Duncan SR, Branch RA, Chang CC, Zhang Y, Leader JK, Gur D, Greenspan SL, Sciruba FC: **Radiographic emphysema predicts low bone mineral density in a tobacco-exposed cohort.** *Am J Respir Crit Care Med* 2011, **183**:885–890.
8. Divo M, Cote C, De Torres JP, Casanova C, Marin JM, Pinto-Plata V, Zulueta J, Cabrera C, Zagaceta J, Hunninghake G, Celli B: **Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease.** *Am J Respir Crit Care Med* 2012, **186**:155–161.
9. Budoff MJ, Nasir K, Kinney GL, Hokanson JE, Barr RG, Steiner R, Nath H, Lopez-Garcia C, Black-Shinn J, Casaburi R: **Coronary artery and thoracic calcium on noncontrast thoracic CT scans: comparison of ungated and**

- gated examinations in patients from the COPD gene cohort. *J Cardiovasc Comput Tomogr* 2011, **5**:113–118.
10. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R: **Quantification of coronary artery calcium using ultrafast computed tomography.** *J Am Coll Cardiol* 1990, **15**:827–832.
 11. Romme EA, Murchison JT, Phang KF, Jansen FH, Rutten EP, Wouters EF, Smeenk FW, Van Beek EJ, MacNee W: **Bone attenuation on routine chest CT correlates with bone mineral density on DXA in patients with COPD.** *J Bone Miner Res* 2012, **27**:2338–2343.
 12. Van Popele NM, Mattace-Raso FU, Vliedgenhart R, Grobbee DE, Asmar R, Van der Kuip DA, Hofman A, De Feijter PJ, Oudkerk M, Witteman JC: **Aortic stiffness is associated with atherosclerosis of the coronary arteries in older adults: the rotterdam study.** *J Hypertens* 2006, **24**:2371–2376.
 13. Farrar DJ, Bond MG, Riley WA, Sawyer JK: **Anatomic correlates of aortic pulse wave velocity and carotid artery elasticity during atherosclerosis progression and regression in monkeys.** *Circulation* 1991, **83**:1754–1763.
 14. Demer LL: **Effect of calcification on in vivo mechanical response of rabbit arteries to balloon dilation.** *Circulation* 1991, **83**:2083–2093.
 15. Barr RG, Ahmed FS, Carr JJ, Hoffman EA, Jiang R, Kawut SM, Watson K: **Subclinical atherosclerosis, airflow obstruction and emphysema: the MESA lung study.** *Eur Respir J* 2012, **39**:846–854.
 16. Sverzellati N, Cademartiri F, Bravi F, Martini C, Gira FA, Maffei E, Marchiano A, La VC, De FM, Kuhnigk JM, Rossi C, Pastorino U: **Relationship and prognostic value of modified coronary artery calcium score, FEV1, and emphysema in lung cancer screening population: the MILD trial.** *Radiology* 2012, **262**:460–467.
 17. McAllister DA, MacNee W, Duprez D, Hoffman EA, Vogel-Claussen J, Criqui MH, Budoff M, Jiang R, Bluemke DA, Barr RG: **Pulmonary function is associated with distal aortic calcium, not proximal aortic distensibility, MESA lung study.** *COPD* 2011, **8**:71–78.
 18. MacNee W, Maclay J, McAllister D: **Cardiovascular injury and repair in chronic obstructive pulmonary disease.** *Proc Am Thorac Soc* 2008, **5**:824–833.
 19. Bon J: **Does radiographic emphysema correlate with low bone mineral density?** *Curr Opin Pulm Med* 2012, **18**:125–130.
 20. Ohara T, Hirai T, Muro S, Haruna A, Terada K, Kinose D, Marumo S, Ogawa E, Hoshino Y, Niimi A, Chin K, Mishima M: **Relationship between pulmonary emphysema and osteoporosis assessed by CT in patients with COPD.** *Chest* 2008, **134**:1244–1249.
 21. Jacobs PC, Prokop M, Van der Graaf Y, Gondrie MJ, Janssen KJ, De Koning HJ, Isgum I, Van Klaveren RJ, Oudkerk M, Van GB, Mali WP: **Comparing coronary artery calcium and thoracic aorta calcium for prediction of all-cause mortality and cardiovascular events on low-dose non-gated computed tomography in a high-risk population of heavy smokers.** *Atherosclerosis* 2010, **209**:455–462.
 22. Shaw LJ, Raggi P, Callister TQ, Berman DS: **Prognostic value of coronary artery calcium screening in asymptomatic smokers and non-smokers.** *Eur Heart J* 2006, **27**:968–975.
 23. Mohlenkamp S, Lehmann N, Moebus S, Schmermund A, Dragano N, Stang A, Siegrist J, Mann K, Jockel KH, Erbel R: **Quantification of coronary atherosclerosis and inflammation to predict coronary events and all-cause mortality.** *J Am Coll Cardiol* 2011, **57**:1455–1464.
 24. Karras A, Haymann JP, Bozec E, Metzger M, Jacquot C, Maruani G, Houillier P, Froissart M, Stengel B, Guardiola P, Laurent S, Boutouyrie P, Briet M: **Large artery stiffening and remodeling Are independently associated with All-cause mortality and cardiovascular events in chronic kidney disease.** *Hypertension* 2012, **60**:1451–1457.
 25. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM: **Impact of aortic stiffness on survival in end-stage renal disease.** *Circulation* 1999, **99**:2434–2439.
 26. Laurent S, Cockcroft J, Van BL, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H: **Expert consensus document on arterial stiffness: methodological issues and clinical applications.** *Eur Heart J* 2006, **27**:2588–2605.
 27. Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM: **Stiffness of capacitive and conduit arteries: prognostic significance for end-stage renal disease patients.** *Hypertension* 2005, **45**:592–596.
 28. Celli BR, Locantore N, Yates J, Tal-Singer R, Miller BE, Bakke P, Calverley P, Coxson H, Crim C, Edwards LD, Lomas DA, Duvoix A, MacNee W, Rennard S, Silverman E, Vestbo J, Wouters E, Agusti A: **Inflammatory biomarkers improve clinical prediction of mortality in chronic obstructive pulmonary disease.** *Am J Respir Crit Care Med* 2012, **185**:1065–1072.
 29. Van der Klift M, Pols HA, Geleijnse JM, Van der Kuip DA, Hofman A, De Laet CE: **Bone mineral density and mortality in elderly men and women: the Rotterdam study.** *Bone* 2002, **30**:643–648.
 30. Szulc P, Maurice C, Marchand F, Delmas PD: **Increased bone resorption is associated with higher mortality in community-dwelling men > or = 50 years of age: the MINOS study.** *J Bone Miner Res* 2009, **24**:1116–1124.

doi:10.1186/1465-9921-14-129

Cite this article as: Romme et al.: Associations between COPD related manifestations: a cross-sectional study. *Respiratory Research* 2013 **14**:129.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

