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Quantitative CT evidence of airway inflammation in WTC workers and volunteers with low FVC spirometric pattern

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Abstract

Background—The most common abnormal spirometric pattern reported in WTC worker and volunteer cohorts has consistently been that of a nonobstructive reduced forced vital capacity (low FVC). Low FVC is associated with obesity, which is highly prevalent in these cohorts. We used quantitative CT (QCT) to investigate proximal and distal airway inflammation and emphysema in participants with stable low FVC pattern.

Methods—We selected study participants with at least two available longitudinal surveillance spirometries, and a chest CT with QCT measurements of proximal airway inflammation (wall area

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Authors' contributions:

RED, RSJ, and JCC designed and oversaw the study and guided the analytical strategies. JW and JTD performed all statistical analyses. APR and RSJ established the WTC Chest CT Imaging Archive, appraised chest CT scan study quality for QCT, and APR performed the QCT measurements. All authors contributed to writing, and reviewed and revised the draft and the final manuscript.

Statement of Ethics:

This study complied with the guidelines for human studies in accordance with the World Medical Association Declaration of Helsinki. The Mount Sinai Program for the Protection of Human Subjects (IRB 18 00603) reviewed and approved the study protocol, with waiver of informed consent.

percent, WAP), end-expiratory air trapping, suggestive of distal airway obstruction (expiratory to inspiratory mean lung attenuation ratio, MLA_{EI}), and emphysema (percentage of lung volume with attenuation below −950 HU, LAV%). The comparison groups in multinomial logistic regression models were participants with consistently normal spirometries, and participants with stable fixed obstruction (COPD).

Results—Compared to normal spirometry participants, and after adjusting for age, sex, race/ethnicity, BMI, smoking, and early arrival at the WTC disaster site, low FVC participants had higher WAP (OR_{adj} 1.24, 95% CI 1.06, 1.45, per 5% unit), suggestive of proximal airway inflammation, but did not differ in MLA_{EI}, or LAV%. COPD participants did not differ in WAP with the low FVC ones and were more likely to have higher MLA_{EI} or LAV% than the other two subgroups.

Discussion—WTC workers with spirometric low FVC have higher QCT-measured WAP compared to those with normal spirometries, but did not differ in distal airway and emphysema measurements, independently of obesity, smoking, and other covariates.

Keywords

multidetector computed tomography; Computer Assisted Image Processing; Obesity; bronchial diseases; smoke inhalation injury; World Trade Center Attack, 2001; Spirometry; forced vital capacity; Obstructive airway disease; Occupational Airways and Lung Diseases

Introduction

The low FVC or “restrictive” (as opposed to obstructive) spirometric ventilatory impairment has consistently and by far been the predominant abnormal spirometric pattern in the World Trade Center (WTC) disaster occupationally exposed population. Reported prevalences have been in the order of 20.5 to 28.8%[1–4], which exceed the 8.2% and 7.1% estimates among participants aged 40–59 in the National Health and Nutrition Examination Survey (NHANES) in 1988–1994, and 2007–2010, respectively[5], and those reported in several other studies in countries with developed economies[6]. This type of impairment is defined by the presence of a reduced forced vital capacity (FVC) without obstruction (i.e., with a normal ratio of first-second forced expiratory volume to FVC, FEV_1/FVC). Although describing it as “low FVC” would be most accurate (as we will do henceforth), this spirometric ventilatory impairment pattern has received over many years a variety of names and slightly different definitions, such as restrictive[7,8], GOLD-unclassified (GOLD-U)[9], preserved ratio-impaired spirometry(PRISM)[10,11], nonspecific[12,13], or pseudorestrictive[14,15] pattern.

Although low FVC is considered a manifestation of airway obstruction according to modern spirometry interpretative guidelines[7], this is controversial, as is not commonly considered *per* se typical or diagnostic of common chronic obstructive airway diseases such as asthma or COPD. Furthermore, low FVC can also result from a variety of factors, including obesity[16] (more prevalent in the WTC occupational cohorts[17–19,4] than in the general U.S. population[20]), poor expiratory effort, and true lung restriction (i.e., reduced total lung capacity)[21]. While low FVC is most often a stable pattern, it can also be a transitional

stage to or from chronic obstructive pulmonary disease (COPD)[22], and, importantly, is associated with functional limitations similar to those of moderate COPD[10].

Quantitative chest CT (QCT) has provided tools to characterize airway and parenchymal lung disorders[23]. We have gathered a large number of chest CT studies in one of the main WTC occupational cohorts[4,24]. The aim of this study was thus to examine quantitative chest CT (QCT) metrics of proximal airway inflammation, end-expiratory air trapping (suggestive of distal airway obstruction[25]), and emphysema[26] in WTC exposed participants with low FVC spirometric pattern, in comparison to equally exposed participants with normal spirometries, and those stably meeting the spirometric definition of chronic obstructive pulmonary disease (COPD).

Methods

Study Population and Data Acquisition

Our study population consisted of workers who participated in the rescue, recovery, cleanup, and restoration of the WTC site from September 11, 2001 to June 2002, and were screened and enrolled in research at the Mount Sinai WTC Clinical Center in New York City[2,27]. The screening and recruitment tools have been reported previously[2]. Participants, enrolled as early as April 2002, were initially evaluated at the time of entry into the cohort, and subsequently at 12- to 18-month intervals. Details of the periodic evaluations have been reported elsewhere, but included review of symptoms, occupational exposures, diseases, physical examination, spirometry, laboratory tests, and biennial chest radiograph[2]. This study involved a sub-cohort of participants additionally evaluated by the WTC Pulmonary Evaluation Unit who also had chest CT imaging performed[4], and at least 2 periodic spirometries with bronchodilator response (BDR) testing.

All spirometries for this study were performed using the EasyOne® portable flow device (ndd Medizintechnik, Zurich, Switzerland). Bronchodilator response (BDR) was assessed by repeating spirometry 15 minutes after administration of 180 mcg of albuterol via metered dose inhaler and a disposable spacer. This was done most often at the baseline examination, and independently from clinical status. Predicted values for spirometric measurements were calculated for all participants' acceptable tests, based on reference equations from the third phase of the NHANES[28]. All testing, quality assurance, ventilatory impairment pattern definitions, bronchodilator response presence, and interpretative approaches followed American Thoracic Society recommendations[29,30,7,31]. Spirometries in this study were selected if performance had been acceptable, and they had a good quality, based both on computer quality grade (a measure of reproducibility across trials)[31] A or B, or C if at least 5 trials had been obtained, and, importantly, the forced exhalatory time was at least 6 seconds[30,6].

As previously reported[4,24], all chest CT studies were performed at Mount Sinai Hospital in General Electric® or Siemens® multidetector row chest CT scanners. Chest CT studies were performed using a protocol[25] with a radiation dose at 120 kVp, and a mean of 146 (SD 69) mAs, with subjects in the supine position, from the lung apices to the bases in a single breath hold at maximum inspiration, with no contrast, and with section thickness not

exceeding 3 mm. All deidentified and coded chest CT images were stored and catalogued during the past 7 years in the WTC PEU Chest CT Image Archive (ClinicalTrials.gov identifier NCT03295279). CT scans were selected to have adequate quality study for quantitative chest CT scan (QCT) measurements performed with the Simba system (http://www.via.cornell.edu/simba/simba)[32,33,24,34].

Measurements

Our outcomes of interest were three groups of participants selected and classified according to their spirometric pattern: (1) participants who had consistently normal spirometry (no restriction or obstruction, or evidence of bronchodilator response at any time, BDRany); (2) participants with FVC below their individual lower limit of normal (FVC<LLN) and no obstruction (i.e., their FEV_1/FVC>LLN) in all of their spirometries[7,8]; and (3) participants with stable COPD spirometry pattern[35], defined as 2 or more spirometries with fixed obstruction (i.e., post-bronchodilator FEV_1/FVC ratio <0.7), and no record of a normal or a low FVC spirometry. Spirometric grade was defined as recommended[35] for descriptive purposes.

Our primary predictors of interest were three QCT measures of proximal and distal conducting airway disease, and emphysema[26] in each participant's first available CT, measured by the Simba system (http://www.via.cornell.edu/simba/simba)[33,32]. As an indicator of emphysema, we used the percent of lung volume with attenuation <−950 HU (low attenuation volume percent, LAV%). We used 2.5% as a cut point, based on previously published QCT findings in a nonsmoking healthy multiethnic population[36]. As an indicator of end-expiratory air trapping, and presumably distal airway disease, we used the expiratory to inspiratory chest CT ratio of mean lung attenuation ratio (MLA_{EI}), with cut point of 87.4%, based on previously published data[37]. Finally, as an indicator of proximal airway disease, we used wall area percent (WAP) of the 3rd generation (segmental) bronchus of the right upper lobe, as a continuous variable in units of 5%[24]. A higher WAP suggests airway wall thickening, in relation to the lumen, which is in turn suggestive of airway inflammatory changes.

Covariates of interest included age at baseline examination, sex, race/ethnicity, body mass index (BMI), early arrival at WTC site (an indicator of WTC occupational exposure indicator, and defined dichotomously as arrival within 48 hours of the disaster[3,38]), baseline smoking status and intensity (in pack-years), pre-WTC occupational exposures, and occupation on 9/11/2001, as described previously[4]. Race/ethnicity was categorized as Latino of any race, non-Latino black/other ethnicity, English speaking and Polish speaking non-Latino White[4]. For descriptive purposes, we estimated the annual prevalence of current smoking for the study population for the years ending in June 2003 and June 2018.

Statistical analyses

Descriptive statistics included mean and standard deviation (SD), or median and interquartile ranges (IQR) for normally, and non-normally distributed continuous variables, respectively, and counts and proportions for categorical variables. Since some variables were missing >10% of the data, the latter were imputed using the fully conditional specification

method (chained equations), to create 15 imputations of the original dataset. Unadjusted analyses were performed using simple logistic regression. Multinomial logistic regression was then performed with the three spirometrically defined categories as outcomes, and models created for each of the three primary QCT predictors (WAP, MLA_{EI}, and LAV%), respectively. We chose adjusting covariates based on clinical relevance and previous work. Collinearity was excluded by the variance inflation factor method. Covariates were eliminated to prevent model overfitting by testing for evidence of effect measure modification (by change in estimate of primary predictor >10%) and removing those by smallest effect-estimate first, and testing for change in model fit. Model fit was examined using deviance/Pearson's goodness of fit and average c statistic among the 15 imputations. All analyses were performed using SAS v.9.4 (SAS institute, Cary, NC).

Results

Figure 1 shows the study flow chart. Of the 1641 participants with images in the WTC Chest Imaging Archive, 1592 had at least 2 spirometries as of June 30, 2018, and 640 patients fit our above described stable spirometric pattern outcome definitions, and constituted our final study population. Each study participant had a median of 6 (IQR 4–7) spirometries, and their chest CT scan was performed a median of 8.75 (IQR 7.1–10.25) years after 9/11/2001. As shown in Table OS1, and compared to those excluded, participants included in the study had very slightly larger proportions of never smokers, men, and law enforcement workers and laborers, and substantially less evidence of BDR at any time.

Of our study sample, 59 participants met our spirometric definition of COPD, 414 participants had consistently normal spirometries, and 167 participants consistently had low FVC. Table 1 shows the characteristics of our study population and the three subgroups. As in previous reports, participants were predominantly (84%) male, aged 45 years (SD 9 years) at baseline, and had an average BMI of 29.1 (SD 4.5) kg/m^2, consistent with previous reports[17–19,4] on WTC occupational cohorts of prevalence of overweight and obesity exceeding contemporary national averages[20]. Only 17.5% were current smokers at their baseline evaluation, and the yearly prevalence of current smoking declined fairly steadily from 20.8% in the year ending in June 2003, to 7.3% in the year ending in June 2018. Bronchodilator response was evident at any given time in 48 (29%) of the low FVC, and 44 (75%) of the COPD subgroup participants. The spirometric severity of the COPD participants was mild in 20, moderate in 36, severe in 3, and very severe in none of them. Compared to the normal subgroup, the low FVC subgroup tended to have a higher BMI and proportion of nonsmokers, of workers arriving early at the WTC site, of Latino ethnicity, and of participants with law enforcement pre-WTC occupations. Participants with COPD tended to be older, more likely to be English speaking non-Latino/White, have a higher proportion of ever smokers and more smoking pack-years but, notably, approximately one third denied having ever smoked before 9/11/2001.

Table 2 presents the unadjusted and adjusted comparisons of the three groups, by each of the three QCT metrics. Compared to normal spirometry participants, low FVC participants had higher WAP (OR_{adj} 1.25, 95% CI 1.08, 1.46, per 5% unit), suggestive of proximal airway inflammation, but did not differ in end-expiratory air trapping (MLA_{EI}), or emphysema

(LAV%). WAP did not differ between the low FVC and the COPD subgroups. On the other hand, and as expected, participants with COPD spirometries were significantly more likely to have higher MLA_{EI} and LAV% than both the low FVC and normal spirometry participants.

Discussion

To our knowledge, this study is the first to focus on low FVC, uniformly the most common spirometric abnormality described in the WTC occupational cohorts[1,3,24], and to use QCT measurements for its characterization. The focus on low FVC pattern demands stringent quality criteria for spirometry, including forced exhalatory times of at least 6 seconds[6], which is virtually unprecedented in previous studies with surveillance spirometry data from the largest WTC occupational cohorts. We demonstrated an association of proximal airway inflammation (as suggested by WAP) with a persistent low FVC pattern, even after adjustment for important and relevant covariates, like BMI[39] and smoking. WAP did not seem different between the low FVC and the COPD subgroups, and was higher in both than in the normal subgroup. As expected, COPD participants were more likely to have higher QCT measurements of distal airway inflammation, and emphysema than those of both normal and low FVC spirometry participants.

Our low FVC subgroup had similar characteristics to the GOLD unclassified (GOLD-U) smokers subgroup of COPDGene®[9], including increased BMI and a higher proportion of nonwhite participants, and an increased subsegmental airway wall thickness compared to smoking control participants. Our findings are similar, in a cohort with a >50% proportion of never smokers and steadily declining current smoking prevalence, and adjusting for both smoking and BMI in our models. The predominance of proximal airway abnormalities over more distal involvement suggests chronic bronchitis, is similar to what has been described in subjects with COPD and chronic bronchitis, compared to those without it[40], and lends further support to the clinical diagnosis of nonspecific or nonobstructive chronic bronchitis for a substantial proportion of WTC workers with lower airway disease[3,38]. Of note, our results are independent of obesity, which has a well documented excess prevalence in the WTC occupational cohorts[17–19,4], and a well-known negative association with FVC[16], and positive with WAP[39]. Although pleural thickening is prevalent in about 1 in 5 WTC worker in this cohort[4], there is no consensus on the effect of that finding on FVC in the absence of asbestosis, and our larger previous study did not suggest it[4]. We excluded participants with evidence of bronchodilator response (BDR) at any time from the normal subgroup, because finding BDR would more readily lead, given consistent symptoms, to a clinical classification of asthma. The requirement of at least two spirometries with fixed obstruction to define COPD is in accordance with the known instability of that diagnosis, particularly in mild disease[22,41] like that of our cohort participants, and allowed a confident estimation of the cumulative incidence of COPD in this cohort with chest CT imaging data at 3.6%.

We did not find that QCT-measured emphysema or end-expiratory air trapping were increased in the low FVC compared to the normal spirometry participants. As the distal airways are the main site of the obstruction in COPD[42,43], it is not surprising that low

FVC with proximal airway disease, but without substantial evidence (even if indirect) of small airway disease, or of emphysema, is not associated with spirometric obstruction. Other lines of evidence have suggested, however, that low FVC without obstructive spirometric impairment [44] or in response to bronchial challenge testing[45] may result from loss of lung units in parallel distally to obstructed bronchioles. Unadjusted impulse oscillometric data in a WTC-exposed community resident and worker case series reported evidence of increased distal airway resistance in association with restrictive ventilatory impairment[46].

The strengths of this study relate to the fairly extensive availability of functional and QCT measurements, in well-defined subgroups with stable spirometric patterns, and the high prevalence of the main pattern under study (low FVC).

Our study also had some limitations. QCT measurements lack normative data, but our choices of criteria are reasonable based on reports from selected large studies, and our group definitions allowed the intended comparisons. Categorizations were necessary for MLA_{EI} and LAV%, given the distribution of the data, with large number of participants (even in the COPD subgroup) with normal or very mild abnormalities. Distal airway inflammation is likely to be present in at least some subgroups of individuals with low FVC. Our inability to demonstrate significantly increased QCT end-expiratory air trapping in low FVC vs. normal spirometry participants does not exclude distal airway inflammation, as increased WAP has been demonstrated to predict it[47], and current QCT tools do not measure it directly[26]. We defined our subgroups strictly, based on consistent longitudinal functional data, and excluding many participants who made subgroup transitions. The study of those transitions requires a different methodologic approach[22]. Lastly, we lacked total lung capacity to exclude true restriction in our low FVC subgroup, but aside from infrequent and heterogenous cases, interstitial lung disease (ILD) has not been demonstrated thus far in the large occupational WTC cohorts. Interstitial lung abnormalities are, however, present in some of our workers with chest CT images[4], and long term surveillance will help identify incident cases of ILD.

In conclusion, we demonstrated QCT evidence of proximal airway inflammation in WTC workers with persistent low FVC spirometry pattern, compared to participants with normal spirometries, and independently from obesity and tobacco smoking. This finding supports the plausibility of low FVC as resulting from a chronic inflammatory airway disease presumably resulting of inhaled toxicant exposures. As these cohorts are followed up for years to come, it will be important to appraise the impact of this condition on general health, given the reported associations of low FVC pattern not only with increased prevalence of respiratory symptoms, but with a variety of respiratory[10] and multisystemic functional limitations, medical co-morbidities[48,9,49,8,50], and even mortality risk[51–54].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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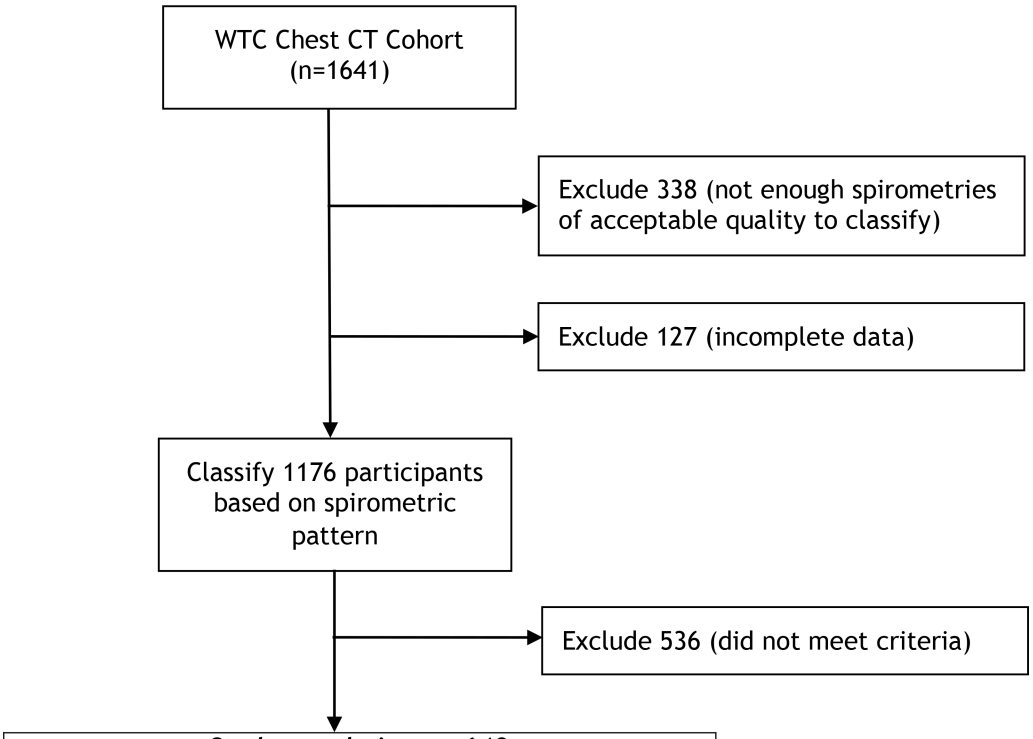

Study population, n=640	
Subgroup	*Criteria*
Low FVC (n=167)	Consistently low FVC spirometries
COPD (n=59)	≥2 fixed obstruction spirometries
Normal (n=414)	Consistently normal spirometries

Figure 1.
Study flow chart.

Table 1:

Characteristics of the study population, and the three spirometrically defined subgroups.

Variable*		All Participants	Normal	Low FVC	COPD
n		640	414	167	59
LAV%	median	0.05 (0–0.42)	0.05 (0–0.45)	0.02 (0–0.10)	0.87 (0.14–4.11)
	>2.5%	37 (6)	20 (5)	3 (2)	14 (24)
WAP	median	61.9 (56–41)	60.5 (56–66)	64.6 (59–68)	64.9 (60–72)
MLA_{EI}	median	83.0 (78–87)	83.0 (78–86)	81.0 (75–85)	88.2 (85–92)
	>87.4%	45 (7)	25 (6)	7 (4)	13 (22)
Age	years	45 (9)	45 (9)	46 (9)	50 (9)
Sex	male	538 (84)	339 (82)	146 (87)	53 (90)
	female	102 (16)	87 (18)	21 (13)	6 (10)
BMI	kg/m^2	29.1 (4.5)	28.6 (4.0)	30.5 (5.5)	28.3 (4.4)
Race/ethnicity	non-Latino white	342 (53)	223 (54)	79 (47)	40 (68)
	Latino	238 (37)	159 (38)	67 (40)	12 (20)
	non-Latino black/other	60 (9)	32 (8)	21 (13)	7 (12)
Occupation	Management/services	108 (18)	59 (15)	35 (21)	14 (24)
	Construction trades	114 (19)	69 (18)	35 (21)	10 (17)
	Laborers/cleaners	206 (34)	170 (44)	22 (13)	14 (24)
	Production/Transportation	28 (5)	16 (4)	9 (5)	3 (5)
	Law enforcement	156 (25)	75 (19)	63 (38)	18 (31)
Arrival at	< 48 hours	308 (48)	164 (41)	106 (63)	38 (64)
WTC site	> 48 hours	332 (52)	250 (60)	61 (37)	21 (36)
BDR	at any visit	92 (14)	0 (0)	48 (29)	44 (75)
Smoking	Never	350 (55)	233 (56)	99 (59)	18 (31)
	Current	112 (18)	67 (16)	26 (16)	19 (32)
	Former	178 (28)	114 (28)	42 (27)	22 (37)
Smoking	pack-years	7 (13)	5 (11)	6 (11)	21 (24)

*Presented as n (%), mean (SD), or median (IQR), as appropriate

Table 2.

Unadjusted and adjusted comparisons of the three QCT measurements of emphysema (LAV%, >2.5%) and proximal (WAP, per 5% units), and distal (MLA_{EI}, >87.4%) airway disease, among three spirometrically defined groups. The multinomial logistic regression models were adjusted for age, sex, race/ethnicity, BMI, baseline smoking status and smoking pack-years, and early arrival (within 48 hours) at the WTC disaster site.

QCT metric	Comparison	OR	95% CI	OR_{adj}	95% CI
WAP	Low FVC vs. Normal	1.32	1.15, 1.52	1.25	1.08, 1.46
	COPD vs. Low FVC	1.11	0.87, 1.42	1.13	0.87, 1.47
	COPD vs. Normal	1.47	1.17, 1.85	1.41	1.10, 1.80
MLA_{EI}	Low FVC vs. Normal	0.74	0.37, 1.48	0.85	0.40, 1.79
	COPD vs. Low FVC	6.56	2.69, 16.02	5.64	2.02, 15.76
	COPD vs. Normal	4.83	2.43, 9.60	4.77	2.03, 11.20
LAV%	Low FVC vs. Normal	0.48	0.14, 1.61	0.53	0.15, 1.87
	COPD vs. Low FVC	10.36	2.95, 36.43	7.42	1.94, 28.31
	COPD vs. Normal	4.98	2.40, 10.32	3.94	1.58, 9.82