The association of lung function and pulmonary vasculature volume with cardiorespiratory fitness in the community

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Lower FEV_1, FVC and D_{LCO} were associated with lower exercise capacity, as well as oxygen uptake efficiency slope and ventilatory efficiency. In addition, lower total and peripheral pulmonary blood vessel volume were associated with lower peak V'_{O_2}. https://bit.ly/31VVpsu

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Abstract

Background Cardiorespiratory fitness is not limited by pulmonary mechanical reasons in the majority of adults. However, the degree to which lung function contributes to exercise response patterns among ostensibly healthy individuals remains unclear.

Methods We examined 2314 Framingham Heart Study participants who underwent cardiopulmonary exercise testing (CPET) and pulmonary function testing. We investigated the association of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC and diffusing capacity of the lung for carbon monoxide (D_{LCO}) with the primary outcome of peak oxygen uptake (V'_{O_2}) along with other CPET parameters using multivariable linear regression. Finally, we investigated the association of total and peripheral pulmonary blood vessel volume with peak V'_{O_2}.

Results We found lower FEV_1, FVC and D_{LCO} were associated with lower peak V'_{O_2}. For example, a 1 L lower FEV_1 and FVC was associated with a 7.1% (95% CI 5.1–9.1%) and 6.0% (95% CI 4.3–7.7%) lower peak V'_{O_2}, respectively. By contrast, FEV_1/FVC was not associated with peak V'_{O_2}. Lower lung function was associated with lower oxygen uptake efficiency slope, oxygen pulse slope, V'_{O_2} at anaerobic threshold (AT), minute ventilation (V'_E) at AT and breathing reserve. In addition, lower total and peripheral pulmonary blood vessel volume were associated with lower peak V'_{O_2}.

Conclusions In a large, community-based cohort of adults, we found lower FEV_1, FVC and D_{LCO} were associated with lower exercise capacity, as well as oxygen uptake efficiency slope and ventilatory efficiency. In addition, lower total and peripheral pulmonary blood vessel volume were associated with lower peak V'_{O_2}. These findings underscore the importance of lung function and blood vessel volume as contributors to overall exercise capacity.

Introduction

Exercise capacity as measured by cardiopulmonary exercise testing (CPET) is a powerful predictor of clinical outcomes across both health and disease [1–4]. Global exercise capacity integrates the entire oxygen cascade through which oxygen transits from the mouth to the mitochondria in order to support

performance of physical activity. While studies primarily in referral populations have often related resting pulmonary function testing (PFT) to impairment in exercise capacity among individuals with established lung disease, less is known about the impact of lung structure and function on overall fitness in a relatively healthy community cohort without overt lung disease. Whether the association of resting lung function with exercise capacity is driven by limitations in pulmonary performance, including gas exchange (ventilatory efficiency), or may also be associated with limitations in cardiac performance, including heart rate response or changes in pulmonary vasculature (as measured by pulmonary blood vessel volume), has not been fully explored.

While prior studies have demonstrated that lung function as measured by forced expiratory volume in 1 s (FEV_1) is associated with peak oxygen uptake (V'_{O_2}) in healthy and elderly individuals, the exact contributions of resting pulmonary function to exercise physiology, including cardiac and pulmonary performance, remain incompletely understood [5, 6].

Determining if resting lung function may be associated with specific physiological measures of exercise response as well as lung structure may be of direct clinical relevance. For example, oxygen uptake efficiency slope (OUES), an effort-independent measure that integrates oxygen uptake augmentation and ventilatory response, predicts outcomes in patients with conditions such as heart failure. However, OUES has not been investigated in relation to lung structure and function in a community cohort [7]. Furthermore, ventilatory anaerobic threshold (AT) has been ascribed to cardiovascular limitations in sustaining aerobic metabolism, although the proportion of breathing reserve utilised across PFT distributions in the community remains largely unexplored. In addition, prior studies within the Framingham Heart Study (FHS) cohort have demonstrated that lower FEV_1, forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (D_{LCO}) are associated with lower total and peripheral pulmonary vasculature, although the relationship of pulmonary vasculature to peak V'_{O_2} has not yet been analysed [8].

Thus, we sought to further explore the association of lung function with multidimensional cardiopulmonary exercise response and the relationship of static computed tomography (CT) imaging of total and peripheral pulmonary vasculature volume with peak V'_{O_2}. We hypothesised that lower lung function would be associated with lower cardiorespiratory fitness and that lower total and/or peripheral pulmonary blood vessel volume (which may indicate vascular pruning) would be associated with lower peak V'_{O_2}.

Methods

Study sample

Participants from the FHS who were a part of the Generation Three, Omni Generation Two and New Offspring cohorts were included in this study [9, 10]. Participants without a medical contraindication to exercise underwent CPET during their third examination (2016–2019; n=3117). Among these, 2800 had available PFT performed at the second examination (2008–2011). We excluded participants with submaximal exercise defined as peak respiratory exchange ratio (RER) <1.0 (n=43), history of heart failure (n=1), history of pulmonary embolism (n=6), history of lung cancer (n=7) or missing at least one PFT measurement (n=396) or key outcome values (n=24) or covariates (n=9), resulting in a final sample size of n=2314. In addition, Framingham physical activity index (PAI) was collected on all participants. PAI is a composite score based upon hours spent performing each activity and the weight factor derived from the estimated oxygen consumption for each activity [11]. PAI has been shown to predict incident cardiovascular disease within the FHS [11]. All participants provided informed consent and the study was approved by the Institution Review Boards of Massachusetts General Hospital and Boston Medical Center (Boston, MA, USA).

Cardiopulmonary exercise testing

Participants underwent upright cycle ergometer exercise testing (Lode, Groningen, The Netherlands) and breath-by-breath gas exchange measurement (MedGraphics, St Paul, MN, USA) [12]. After completion of at least 2 min of resting gas exchange measurements, participants performed 3 min of unloaded exercise followed by maximal-effort-limited incremental ramp exercise using 15 or 25 $W \cdot min^{-1}$ ramps [12]. Peak V'_{O_2} values were determined by the highest 30 s median during the final 90 s of exercise. Additional CPET measures are further described in the supplementary material.

PFT and pulmonary blood vessel volume

PFT was conducted during exam cycle 2 [13]. Spirometry and diffusion capacity were performed using the Collins Classic Pulmonary Function Laboratory system (Ferraris Respiratory, Ayer, MA, USA) [12]. Spirometric measurements were performed according to American Thoracic Society standards [14].

In addition to lung function measurements, a subset of the cohort (n=1389) underwent CT scans of the thorax between 2008 and 2011, with further details included in the supplementary material.

Pulmonary blood vessel volumes measured from the same CT scans were available for 867 participants. We measured total blood vessel volume (TBV) within the pulmonary vasculature. The volume of the entire vessel includes the vascular wall and lumen, and includes both arterial and venous vessels. We also measured peripheral pulmonary blood vessel volume (BV5), where small intraparenchymal vessels were defined as <5 mm^2 in cross-sectional area. The ratio of BV5/TBV was calculated as an indicator of vascular pruning [13]. These measures were shown previously to correspond with histological pulmonary vascular volumes [15]. Additional details are included in the supplementary material [13].

Statistical analysis

Baseline clinical characteristics, lung function measures and CPET measures were summarised using frequencies (percentages) or means with standard deviations as appropriate. Cross-sectional associations of lung function (FEV_1, FVC, FEV_1/FVC and D_{LCO}) with CPET measurements were evaluated using multivariable linear regression with peak V'_{O_2} expressed in $mL \cdot kg^{-1} \cdot min^{-1}$ as the primary outcome. Peak V'_{O_2}, V'_{O_2} at AT and oxygen pulse were log transformed to accommodate their skewed distributions and heteroscedasticity. In addition, least squares means (LSMEANs) of peak V'_{O_2} adjusted for age, sex, height and weight across quartiles of lung function were calculated.

All lung function measures and CPET outcomes were standardised (to mean 0, variance 1) to facilitate effect size comparison across variables. The analyses were adjusted for age, sex, smoking status (never, former or current), hypertension (defined as use of hypertension medications, or systolic blood pressure ⩾130 mmHg or diastolic blood pressure ⩾80 mmHg), height (inches), weight (kg), diabetes mellitus (defined as fasting glucose ⩾126 $mg \cdot dL^{-1}$, nonfasting glucose ⩾200 $mg \cdot dL^{-1}$ or the use of antidiabetic medications) and Framingham cohort (Generation Three, Omni Generation Two and New Offspring).

In exploratory analysis, cross-sectional associations of CT-based measures of lung blood vessel volumes with peak V'_{O_2} were performed using multivariable linear regression (adjusted for the same covariates as in the primary analysis). p-values were adjusted using a Bonferroni correction to address multiple testing and were evaluated at a 5% level of significance. In addition, LSMEANs of peak V'_{O_2} adjusted for age, sex, height and weight across quartiles of lung blood vessel volumes were calculated. Analyses were conducted using R version 4.0.3 (www.rproject.org) and SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

We studied a total of 2314 participants; mean age 54±9 years and 54% women. Clinical characteristics are described in table 1. In brief, mean BMI was 28±5 $kg \cdot m^{-2}$; 48% had hypertension and 8% had diabetes mellitus. With regard to smoking status, 33% were former smokers and 6% were current smokers. The majority of the participants had normal lung function with mean FEV_1 102±14% predicted, FVC 105±13% predicted, FEV_1/FVC 0.77±0.06 and D_{LCO} 97±14% predicted.

Lower lung function is associated with lower exercise capacity

During CPET, participants achieved mean maximum heart rate 91% predicted with a mean RER of 1.22, indicating maximal effort exercise. Across all participants, mean peak V'_{O_2} was 22.9±6.8 $mL \cdot kg^{-1} \cdot min^{-1}$ and the majority (98%) exercised to a normal breathing reserve (>20%). In this setting we found that lower FEV_1 was associated with lower exercise capacity. For example, the LSMEAN of peak V'_{O_2}, adjusted for age, sex, height and weight, was 20.3 (95% CI 19.9–20.7) $mL \cdot kg^{-1} \cdot min^{-1}$ in the lowest quartile and 23.7 (95% CI 23.1–24.2) $mL \cdot kg^{-1} \cdot min^{-1}$ among participants in the highest quartile of FEV_1 ($p_{trend} \leqslant 0.001$) (figure 1). Similarly, lower FVC and D_{LCO} were associated with worse peak V'_{O_2} ($p_{trend} \leqslant 0.001$). By contrast, peak V'_{O_2} appeared similar across FEV_1/FVC quartiles.

We next examined the association of continuous lung function measures and peak V'_{O_2} using multivariable regression models. We found that lower FEV_1, FVC and D_{LCO} were associated with lower peak V'_{O_2} and peak V'_{O_2} % pred with multivariable adjustment (table 2). For example, a 1 L lower FEV_1 and FVC was associated with a 7.1% (95% CI 5.1–9.1%) and 6.0% (95% CI 4.3–7.7%) lower peak V'_{O_2}, respectively. Similarly, a 5 $mL \cdot min^{-1} \cdot mmHg^{-1}$ lower D_{LCO} was associated with a 7.1% (95% CI 15.9–8.2%) lower peak V'_{O_2}. FEV_1/FVC was not statistically significantly associated with peak V'_{O_2} (figure 2). In a sensitivity analysis including only participants with peak V'_{O_2} >85% predicted (n=1560), similar associations were found, with lower FEV_1, FVC and D_{LCO} associated with lower peak V'_{O_2} after adjustment for confounders. In addition, after excluding individuals with restrictive lung disease, the association of FEV_1, FVC and D_{LCO} with peak V'_{O_2} was similar. To assess the sensitivity of our estimates

TABLE 1 Baseline participant characteristics (n=2314)

Clinical characteristics	
Age (years)	54±9
Caucasian	2110 (91)
BMI ($kg \cdot m^{-2}$)	28.2±5.4
Smoking status	
Never	1420 (61)
Former	758 (33)
Current	136 (6)
Hypertension	1104 (48)
Diabetes mellitus	177 (8)
Emphysema on imaging	65 (5)
ILA on imaging	20 (1)
Physical activity (PAI[#])	34±6
PFT measures	
FEV_1 (L)	3.40±0.76
FEV_1 % pred	102±14
FVC (L)	4.43±0.99
FVC % pred	105±13
FEV_1/FVC	0.77±0.06
FEV_1/FVC % pred	95±7
D_{LCO} ($mL \cdot min^{-1} \cdot mmHg^{-1}$)	26.29±6.06
D_{LCO} % pred	97±14
CPET measures	
Peak V'_{O_2} ($mL \cdot kg^{-1} \cdot min^{-1}$)	22.9±6.80
OUES ($mL \cdot min^{-1} \cdot log(L \cdot min^{-1})^{-1}$)	1969±582
V'_{O_2} at AT ($mL \cdot kg^{-1} \cdot min^{-1}$)	12.6±3.6
Peak V'_{O_2} % pred	95.5±19.9
Aerobic efficiency ($mL \cdot W^{-1} \cdot min^{-1}$)	8.95±0.95
V'_{O_2}/work ($mL \cdot min^{-1} \cdot W^{-1}$)	10.96±1.0
Peak Borg score	6.81±1.84
Maximum HR % pred	91±10
V'_E at AT ($L \cdot min^{-1}$)	24.7±7.50
Peak RER	1.22±0.10
Oxygen pulse slope (V'_{O_2}/HR)	19.3±7.40
Breathing reserve at AT (%)	79.0±5.2
Breathing reserve at peak exercise (%)	43.3±15.24

Data are presented as mean±SD or n (%). BMI: body mass index; ILA: interstitial lung abnormality; PAI: physical activity index; PFT: pulmonary function testing; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; CPET: cardiopulmonary exercise testing; V'_{O_2}: oxygen uptake; OUES: oxygen uptake efficiency slope; HR: heart rate; V'_E: minute ventilation; AT: anaerobic threshold; RER: respiratory exchange ratio. [#]: PAI is a composite score of hours spent performing an activity and weighted oxygen consumption of the activity as previously described by KANNEL and SORLIE [11].

to smoking status, we removed current and former smokers and the results were similar, with lower FEV_1, FVC and D_{LCO} associated with lower peak V'_{O_2}.

In order to investigate physical activity as a potential confounder, we performed additional analyses accounting for PAI in multivariable models. We found similar findings as the main analysis, with lower FEV_1, FVC and D_{LCO} associated with lower peak V'_{O_2}. In addition, to further address the effect of age, we assessed age by quartile within the cohort and fit a model with an interaction between the age quartiles and pulmonary function (FEV_1, FVC and D_{LCO}). For the pulmonary function variables, the interaction with age was not significant (supplementary table S1).

Reduced breathing reserve is associated with higher peak V'_{O_2}

Interestingly, participants with a reduced breathing reserve (⩽20%; n=180) had a higher peak V'_{O_2} compared with those with a preserved breathing reserve (>20%; n=2134), with mean peak V'_{O_2} 31.2±6.8 and 22.2±6.3 $mL \cdot kg^{-1} \cdot min^{-1}$, respectively. The reduced breathing reserve group had a slightly higher FEV_1 at 3.54 L (*versus* 3.39 L), demonstrating the reduced breathing reserve is being driven more by a higher minute ventilation (V'_E) rather than a lower maximum voluntary ventilation (MVV). Among the sample studied, 187 (8%) met criteria for obstructive lung disease and 53 (2%) met criteria for restrictive lung

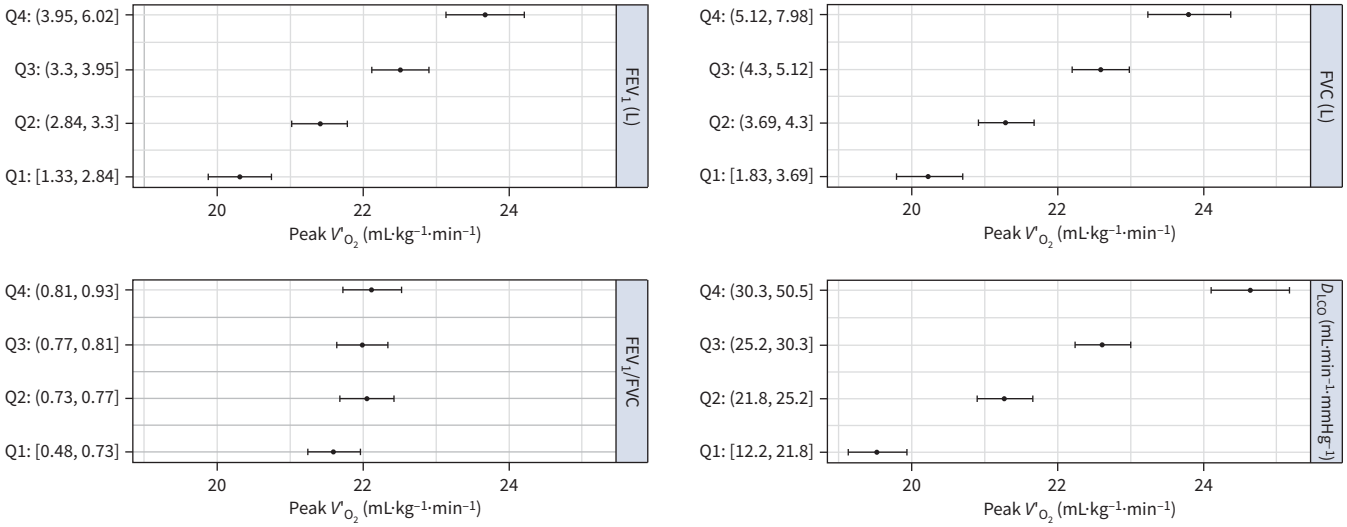

FIGURE 1 Peak oxygen uptake (V'_{O_2}) across quartiles (Q) of lung function measurements. Forest plots displaying the peak V'_{O_2} least squares means adjusted for age, sex, height and weight across quartiles of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC and diffusing capacity of the lung for carbon monoxide (D_{LCO}). The black data points represent the quartile mean peak V'_{O_2} (with 95% CI).

disease. For participants who met criteria for Global Initiative for Chronic Obstructive Lung Disease Stage 1 (n=140) and 2 (n=47), mean peak V'_{O_2} was 22.9±7.02 and 19.3±5.9 mL·kg^{-1}·min^{-1}, respectively. By contrast, those with restrictive lung disease (n=53) had mean peak V'_{O_2} 17.4±3.8 mL·kg^{-1}·min^{-1}.

As a sensitivity analysis, peak breathing reserve was compared between individuals with RER <1.0 (n=43) and RER >1.0 (n=2314) with the mean as 65.8±15.2% and 43.3±10.1%, respectively.

Lower lung function is associated with lower cardiopulmonary performance during exercise

In secondary analyses, using multivariable adjusted linear regression analyses, we examined the relationship of lung function with other metrics of cardiopulmonary function with exercise. We found that lower FEV_1, FVC and D_{LCO} were associated with lower OUES and oxygen pulse slope (table 2). With respect to chronotropic response, we found that lower D_{LCO} was associated with lower heart rate % pred achieved, whereas none of the spirometry-based measures were associated with heart rate response.

TABLE 2 Association of lung function with cardiopulmonary exercise testing (CEPT) variables

	FEV_1			FVC			FEV_1/FVC			D_{LCO}		
	β estimate	SE	p-value	β estimate	SE	p-value	β estimate	SE	p-value	β estimate	SE	p-value
Peak V'_{O_2}	0.18	0.03	<0.001	0.20	0.03	<0.001	0.02	0.02	>0.99	0.28	0.02	<0.001
OUES	0.12	0.02	<0.001	0.14	0.03	<0.001	−0.001	0.01	>0.99	0.28	0.02	<0.001
Peak V'_{O_2} % pred	0.25	0.04	<0.001	0.27	0.04	<0.001	0.02	0.02	>0.99	0.40	0.03	<0.001
V'_{O_2} at AT	0.13	0.03	<0.001	0.16	0.03	<0.001	−0.004	0.02	>0.99	0.30	0.03	<0.001
Oxygen pulse slope	0.09	0.03	0.008	0.10	0.03	0.007	0.003	0.01	>0.99	0.16	0.02	<0.001
V'_{O_2}/work	−0.07	0.03	0.99	−0.06	0.03	>0.99	−0.02	0.02	>0.99	0.05	0.03	>0.99
HR % pred	0.09	0.04	0.53	0.11	0.04	0.143	−0.01	0.02	>0.99	0.19	0.03	<0.001
V'_E at AT	0.16	0.03	<0.001	0.20	0.03	<0.001	−0.01	0.02	>0.99	0.22	0.03	<0.001
Peak RER	0.08	0.04	>0.99	0.02	0.04	>0.99	0.06	0.02	0.11	−0.09	0.03	0.45
BR at AT	0.75	0.03	<0.001	0.59	0.04	<0.001	0.25	0.02	<0.001	−0.03	0.03	>0.99
BR at peak	0.51	0.03	<0.001	0.40	0.04	<0.001	0.17	0.02	<0.001	−0.04	0.03	>0.99

V'_{O_2}: oxygen uptake; OUES: oxygen uptake efficiency slope; AT: anaerobic threshold; HR: heart rate; V'_E: minute ventilation; RER: respiratory exchange ratio; BR: breathing reserve. Analyses were adjusted for age, sex, smoking status (never, current and former), hypertension, height (inches), weight (kg), diabetes mellitus and Framingham cohort. p-values include Bonferroni correction to account for multiple testing and were evaluated at a 5% level of significance. Effect size (β) represents the standard deviation difference in response variable (CPET measures) per 1 SD change in predictor variable (raw lung function measure).

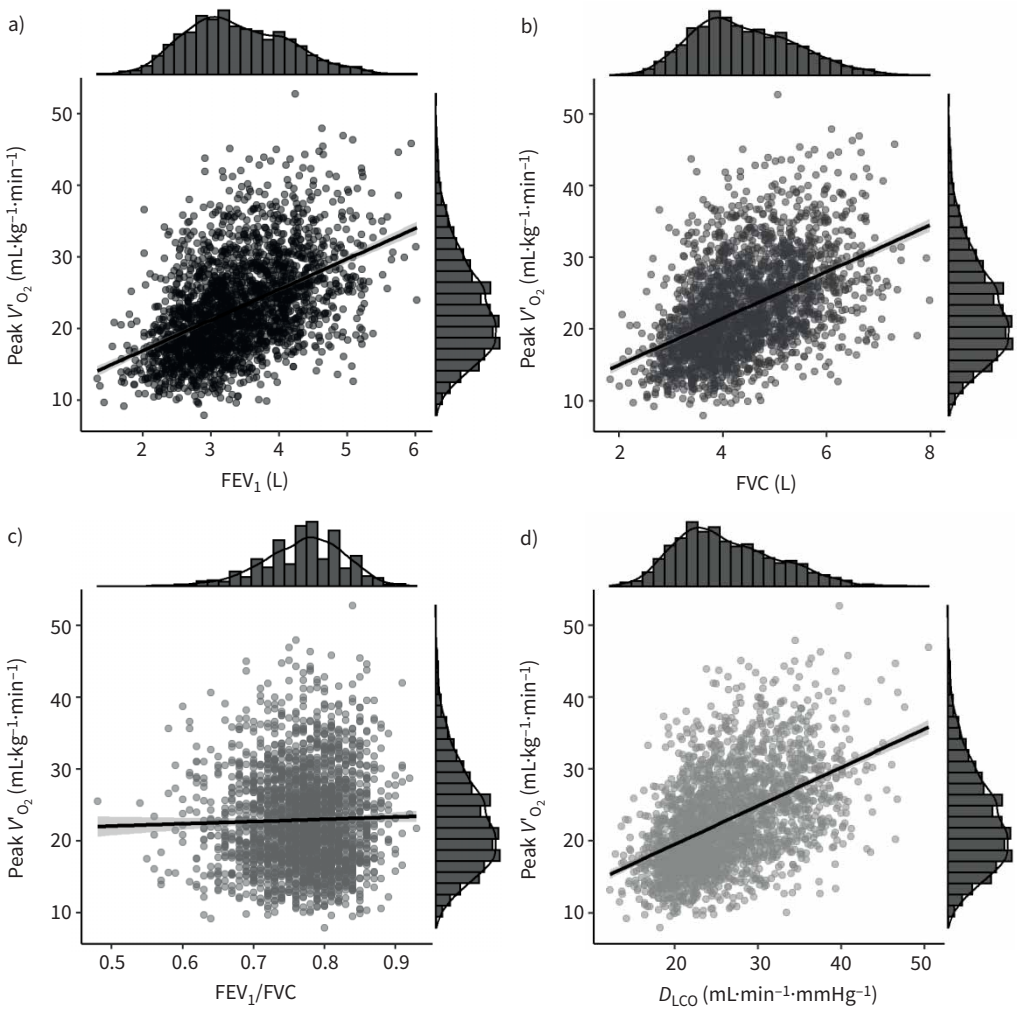

FIGURE 2 Unadjusted associations of lung function measurements with peak oxygen uptake (V'_{O_2}). Scatter plots displaying the relationship of peak V'_{O_2} with a) forced expiratory volume in 1 s (FEV_1), b) forced vital capacity (FVC), c) FEV_1/FVC and d) diffusing capacity of the lung for carbon monoxide (D_{LCO}). Raw data display of lung function measurements with relative peak V'_{O_2} with the data points representing individual participants An unadjusted linear fit to the data points is included with 95% confidence bands. Histograms of each variable are included on the margins.

When examining respiratory performance, lower FEV_1, FVC and D_{LCO} were associated with lower V'_{O_2} at AT and V'_E at AT ($p<0.001$ for all). In addition, lower FEV_1, FVC and FEV_1/FVC were associated with lower breathing reserve at AT and peak ($p<0.001$ for all). These results are not unexpected, as FEV_1 is utilised for MVV calculation and V'_E is a parameter in the breathing reserve equation.

Lower pulmonary blood vessel volume and emphysema on CT imaging is associated with lower peak V'$_{O_2}$

Among the subset of n=1389 with CT measures, we found very few participants with evidence of radiographic abnormalities in lung parenchyma. This included 65 participants with evidence of emphysema on CT imaging with mean peak V'_{O_2} 20.8±5.3 mL·kg^{-1}·min^{-1} compared with 22.5±6.7 mL·kg^{-1}·min^{-1} for those without disease (n=860). There were 20 participants with interstitial lung abnormalities on CT imaging, with mean peak V'_{O_2} 23.1±7.9 mL·kg^{-1}·min^{-1}, similar to those without disease (n=905) (22.4±6.6 mL·kg^{-1}·min^{-1}).

When pulmonary blood vessel volume was examined, those in the lower quartile of TBV and peripheral blood vessel volume (BV5) had lower peak V'_{O_2} LSMEANs (TBV lowest quartile LSMEAN 20.0 (95% CI

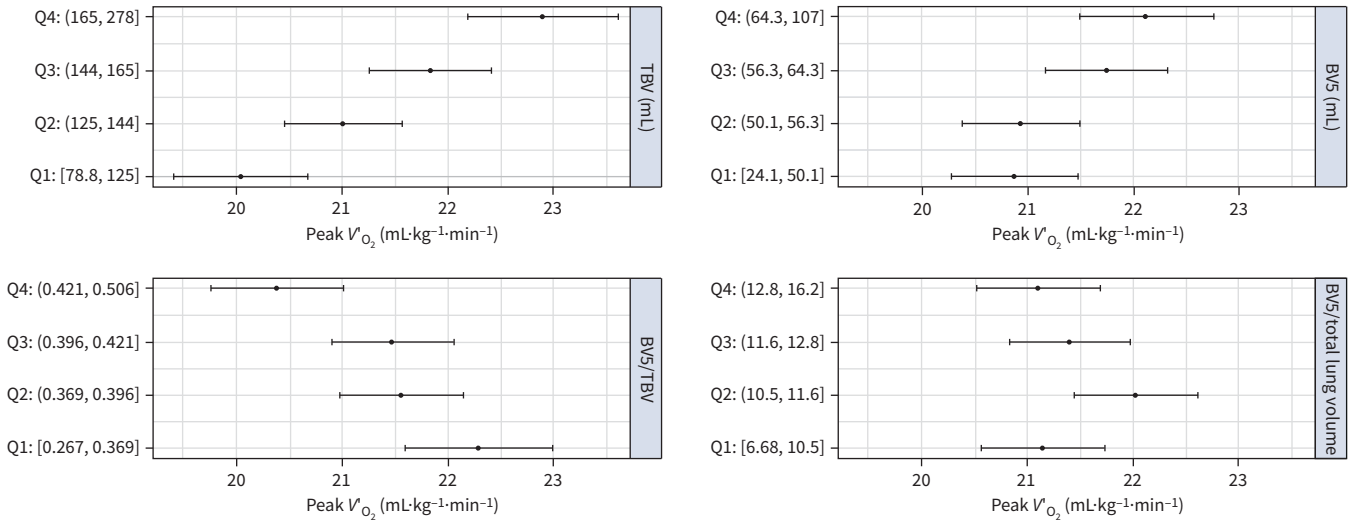

FIGURE 3 Peak oxygen uptake (V'_{O_2}) across quartiles (Q) of computed tomography pulmonary vasculature volumes. Forest plots displaying the peak V'_{O_2} least squares means adjusted for age, sex, height and weight across quartiles of peripheral pulmonary blood vessel volume (vessels <5 mm^2 in cross-sectional area) (BV5), total pulmonary blood vessel volume (TBV), BV5/TBV and BV5/total lung volume. The black data points represent the quartile mean peak V'_{O_2} (with 95% CI).

19.4–20.7) mL·kg^{-1}·min^{-1}; BV5 lowest quartile LSMEAN 20.9 (95% CI 20.3–21.5) mL·kg^{-1}·min^{-1}) compared with the highest quartile (TBV highest quartile LSMEAN 22.9 (95% CI 22.2–23.6) mL·kg^{-1}·min^{-1}; BV5 highest quartile LSMEAN 22.1 (95% CI 21.5–22.8) mL·kg^{-1}·min^{-1}; p<0.001 for both) (figure 3). In regression analysis, a 1 mL lower TBV was associated with a 0.18% (95% CI 0.12–0.24%) lower peak V'_{O_2} and a 1 mL lower BV5 was associated with a 0.29% (95% CI 0.15–0.43%) lower peak V'_{O_2} (table 3). In addition, each 1 SD lower BV5/TBV was associated with a higher peak V'_{O_2}, although no relationship was seen with BV5/total lung volume and peak V'_{O_2}.

In order to investigate physical activity as a potential confounder, we performed additional analyses accounting for PAI in multivariable models. We found similar findings as in the main analysis, with lower TBV and BV5 associated with lower peak V'_{O_2}.

In addition, to further address the effect of age, we assessed age by quartile within the cohort and fit a model with an interaction between the age quartiles and pulmonary blood vessel measurements (BV5 and TBV). For the pulmonary blood vessel measurements variables, the interaction with age was not significant (supplementary table S1).

Discussion

The primary findings in this study are three-fold. First, among a large sample of community-dwelling adults, we found that lower lung function as ascertained by FEV_1, FVC and D_{LCO} was associated with lower exercise capacity. By contrast, there was no association of FEV_1/FVC with exercise capacity,

TABLE 3 Association of pulmonary vasculature volumes with peak oxygen uptake (V'_{O_2}) and oxygen uptake efficiency slope (OUES)

	TBV			BV5			BV5/TBV			BV5/total lung volume		
	β estimate	SE	p-value	β estimate	SE	p-value	β estimate	SE	p-value	β estimate	SE	p-value
Peak V'_{O_2}	0.18	0.03	<0.001	0.11	0.027	<0.001	−0.09	0.03	0.007	−0.02	0.02	0.54
OUES	0.2	0.03	<0.001	0.13	0.024	<0.001	−0.08	0.03	0.005	−0.01	0.02	0.70

TBV: total pulmonary blood vessel volume; BV5: peripheral pulmonary blood vessel volume (vessels <5 mm^2 in cross-sectional area). Analyses were adjusted for age, sex, smoking status (never, current and former), hypertension, height (inches), weight (kg), diabetes mellitus and Framingham cohort. Effect size (β) represents the standard deviation difference in dependent variable (peak V'_{O_2} or OUES) per 1 SD change in independent variable (blood vessel volume).

suggesting that restrictive but not obstructive physiology may be an important determinant of overall fitness among ostensibly healthy individuals. Second, we found that beyond peak V'_{O_2} as an integrated measure of fitness, lung function measures were also associated with specific aspects of cardiovascular and respiratory performance, including OUES, oxygen pulse slope, V'_{O_2} at AT, V'_E at AT and breathing reserve. These findings indicate that the association of lung function and exercise capacity may be related to multiple specific exercise abnormalities in cardiopulmonary performance, including effort-independent measures and measurements taken prior to peak exercise capacity. Lastly, we found that lower radiographic pulmonary vasculature volume as assessed by TBV and BV5 was also associated with lower exercise capacity. Taken together, these findings suggest that lung function, even within the normal range and with preserved breathing reserve, has an effect on exercise capacity.

These results expand upon prior studies that have demonstrated a positive association between peak V'_{O_2} and FEV_1 in healthy adults and the elderly by demonstrating the association extends to FVC and D_{LCO}, and does not include FEV_1/FVC [5, 6, 16]. Our findings that lower FEV_1 and FVC, demonstrating a restrictive-like physiology, is associated with lower exercise capacity is in agreement with prior studies demonstrating that this pattern of lung function decline in a healthy cohort is associated with higher rates of cardiovascular disease development [17]. For example, healthy participants defined as rapid decliners in FEV_1 and FVC over a 1-year period (average 3% change in spirometry) had a four-fold increased risk in incident heart failure over the same time period [17]. Our results demonstrating an association of lung function with the gold standard measurement for functional capacity, *i.e.* peak V'_{O_2}, further highlight the interplay of cardiac and pulmonary systems as lower cardiorespiratory fitness is associated with higher rates of cardiovascular disease and all-cause mortality, and draws attention to the use of PFT as a key additional element of not only lung disease but early detection of cardiac disease [18].

Given V'_{O_2} can be limited by pulmonary diffusing capacity, maximal cardiac output, oxygen carrying capacity of blood or peripheral extraction, we examined additional cardiopulmonary exercise variables to help further characterise the interplay of exercise capacity with pulmonary function. We found that lower OUES was associated with lower pulmonary function. OUES has advantages in comparison with peak V'_{O_2}, in that it is an accurate, reproducible and objective measure of functional capacity at submaximal exercise levels [7]. Given OUES and peak V'_{O_2} have previously been shown to be correlated, it is not surprising the same lung function relationships were seen with OUES and peak V'_{O_2}, with the results suggesting that in those who fail to achieve peak performance the lung function measurements are still related to cardiopulmonary performance [7]. We also found that lower FEV_1, FVC and D_{LCO} were associated with lower oxygen pulse slope. This highlights that the relationship between lung function and exercise capacity persists even after adjusting for heart rate.

The relationship of pulmonary diffusion capacity with peak V'_{O_2} may reflect decreased need for ventilation for carbon dioxide and oxygen transfer and/or increased pulmonary capillary blood volume. Indeed, we found that D_{LCO} was related to OUES and that CT scan-based measures of pulmonary blood volume were related to peak V'_{O_2}. To better understand this relationship, we examined the association of pulmonary blood vessel volume with functional capacity. Similar to D_{LCO}, we observed that lower TBV and BV5 were associated with a lower peak V'_{O_2}. However, the magnitude of the association of TBV to peak V'_{O_2} was substantially larger than the association for BV5, which results in the observed inverse association of lower BV5/TBV with higher peak V'_{O_2}. These results indicate that the total detectable blood vessel volume on CT imaging at rest is most strongly linked to higher exercise tolerance; given that the pulmonary circulation must accommodate a five-fold increase in blood flow from rest to peak exercise, TBV may be an indicator of greater vascular capacitance/potential for distensibility [19]. Therefore, a higher TBV at rest may identify individuals with a greater potential for additional vessel recruitment and therefore oxygen extraction with exercise. In addition, the calibre of the pulmonary vasculature has been graded by pulmonary transit of agitated contrast (PTAC) during exercise, with larger vessels having more PTAC [20]. Individuals with greater PTAC at peak exercise have greater peak V'_{O_2}, higher cardiac output and lower pulmonary vasculature resistance [20]. This suggests that when transitioning from resting to exercise, a larger appearance of the total pulmonary vasculature may indicate an increased distensibility during exercise, allowing greater blood flow and reduction in right ventricular afterload. We acknowledge that the current study is not able to ascertain these important physiological aspects of pulmonary vascular function, but rather assessed pulmonary vascular anatomy and volumes as a noninvasive imaging measure. Our findings suggest that a possible explanation for the relationship of lung function with peak V'_{O_2} extends beyond involvement in cardiac output and is related to pulmonary vascular volume at baseline.

To address potential confounding from baseline physical activity, additional analyses including PAI were included in the model, and similar results that lower lung function and lower pulmonary blood vessel

volume were associated with lower peak V'_{O_2} remained. For example, we found that D_{LCO} was related to exercise capacity. As D_{LCO} increases, less V'_E is required to transfer oxygen (OUES) and carbon dioxide (V'_E/carbon dioxide production (V'_{CO_2}) slope), indicating higher efficiency of gas exchange during exercise [12]. D_{LCO} and TBV at rest are indicators of the lung's ability to accommodate blood volume, a property that must acutely adapt during incremental exercise with requisite augmentation of thoracic blood volume to support cardiac output augmentation.

There are some limitations of the study. The FHS allowed us to study the gold standard measurement of cardiorespiratory fitness through collection of peak V'_{O_2}; however, invasive haemodynamic measurements and arterial blood gases were not available. The collection of lung function and structure measurements (years 2008–2011) occurred prior to CPET measurements (years 2016–2019), which would have been expected to bias our results toward the null. Participants were from a predominantly Caucasian background, limiting potential generalisability of the results. Finally, future studies accounting for baseline physical activity using objective measures will be important to better understand the association of lung function and pulmonary blood vessel volume with functional capacity. Strengths of our study include a large cohort of community-dwelling adults with rigorous cardiopulmonary phenotyping including careful measurement of pulmonary function, CPET, and CT imaging of lung parenchyma and pulmonary vascular volumes.

Our findings indicate that a subclinical and subtle decline in lung function can adversely impact exercise capacity as measured by peak V'_{O_2}. While differences in exercise capacity between individuals are often ascribed to cardiac performance alone or degree of exposure to physical activity, our findings frame the importance of investigating the pathobiological underpinnings of how the entire spectrum of lung structure and function impacts functional capacity. Our findings also highlight the importance of promoting lung health, including potential screening and identification of high-risk individuals for functional decline, as a way of optimising peak V'_{O_2}, which is known to be a potent prognostic predictor in referral populations and in the general population. These preventative strategies would include removal of pulmonary toxic behaviours (*e.g.* smoking), as well as exercise programmes focused on respiratory muscle strength.

Conclusions

In a large community-based sample of whom the majority had preserved breathing reserve, we found lower FEV_1, FVC and D_{LCO} were associated with lower peak V'_{O_2}. By contrast, FEV_1/FVC was not associated with peak V'_{O_2}, suggesting a restrictive physiology pattern was more closely tied to functional capacity. Furthermore, we observed that lower FEV_1, FVC and D_{LCO} were associated with integrated measures of both cardiac performance, including OUES and oxygen pulse slope, as well as pulmonary performances, including V'_{O_2} at AT, V'_E at AT and breathing reserve at AT and peak. Lastly, lower total and peripheral pulmonary vasculature volumes as measured by CT imaging were associated with lower peak V'_{O_2}. These findings underscore the importance of lung structure and function as contributors to overall functional capacity, even in the absence of abnormal breathing reserve.

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