Respiratory Medicine (2010) **104**, 1171–1178

available at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/rmed

Sub-clinical left and right ventricular dysfunction in patients with COPD

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Received 23 September 2009; accepted 28 January 2010
Available online 24 February 2010

KEYWORDS
Arterial stiffness;
COPD;
Tissue Doppler echocardiography;
Ventricular dysfunction

Summary
Background: Cardiovascular manifestations in COPD include increased arterial stiffness, ischaemic heart disease, chronic heart failure and cor pulmonale. We hypothesised that sub-clinical right (RV) and left ventricular (LV) dysfunction occurs in patients with COPD, related to the severity of airflow obstruction, arterial stiffness and systemic inflammation.
Methods: Thirty six patients and 14 controls, all free of overt cardiovascular disease underwent tissue Doppler echocardiography, spirometry, measurement of aortic pulse wave velocity (PWV) and venous sampling for inflammatory markers.
Results: Mean LV myocardial strain and strain rate were less in patients than controls, $p < 0.05$. LV isovolumic relaxation time (IVRT) was prolonged in patients (125 ± 15.2 ms) compared with controls (98.2 ± 21.1 ms), $p < 0.01$, indicating LV diastolic dysfunction. The RV free wall strain and strain rate were less in patients than controls, both $p < 0.05$, indicating RV systolic dysfunction. Patients had sub-clinical pulmonary arterial hypertension with a greater RV myocardial relaxation time and Tei index, both $p < 0.01$. Patients with mild airways obstruction had LV and RV dysfunction and evidence of increased RV afterload compared with controls. In multivariate analyses aortic PWV predicted LV IVRT, $p < 0.01$, while FEV_1 predicted RV Tei index and myocardial relaxation time, both $p < 0.01$.

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0954-6111/$ - see front matter
doi:10.1016/j.rmed.2010.01.020

Conclusions: Patients with COPD have sub-clinical left ventricular dysfunction related to arterial stiffness, and right ventricular dysfunction related to airways obstruction. Both right and left ventricular dysfunction are present in patients with mild airways obstruction suggesting that cardiac co-morbidities commence early in the development of COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is associated with considerable morbidity and is predicted to become the third leading cause of death worldwide by 2020.[1,2] Early in the course of the disease respiratory symptoms predominate, while later systemic complications include osteoporosis,[3] loss of fat free mass (FFM)[3] and cardiovascular disease.[4,5] Cardiovascular complications in patients with COPD include cor pulmonale,[6] a 2—3 fold excess cardiovascular event risk even after allowing for confounders such as smoking,[7] and a greater than four fold excess risk of chronic heart failure (CHF).[8]

Arterial stiffness, an independent predictor of cardiovascular outcome[9,10] was increased in patients with COPD, free of cardiovascular disease, suggesting acceleration of age dependent stiffening.[11] It was present even in mild severity airways obstruction, which suggests stiffening develops in early lung disease in parallel with asymptomatic changes in pulmonary arterial pressure and right ventricular function.[12,13] Long-term effects of increased arterial stiffness in COPD are unknown, but might include cardiac adaptations similar to those in normal aging,[14—17] systemic hypertension[18] and diastolic heart failure.[19] Such changes in cardiac structure and function may underlie the increased risk of cardiovascular disease in COPD.

Echocardiographic evaluation of left and right ventricular function in patients with COPD is challenging, mainly due to lung hyperinflation but may be improved using tissue Doppler echocardiography (TDE) to study regional systolic and diastolic function, myocardial and annular velocities and myocardial deformation indices such as strain and strain rate. TDE allows precise and quantitative measurement of myocardial function and can therefore detect sub-clinical changes.[20]

A low FFM is associated with increased morbidity and mortality in patients with COPD,[21,22] and is partly a result of altered protein metabolism, where protein turnover predominates over protein synthesis.[23] Since cardiac muscle is also a protein rich tissue, it may be affected by similar proteolytic processes which may result in loss of cardiac muscle mass and impairment of myocardial function.

We hypothesised that patients with COPD, clinically free of cardiovascular disease, would have sub-clinical left ventricular (LV) and right ventricular (RV) dysfunction related to the severity of airways obstruction, arterial stiffness, systemic inflammation and changes in body composition. To test this we determined ventricular function by echocardiography with tissue Doppler imaging, and related structural and functional changes to these variables in clinically stable patients with a wide range of severity of COPD.

Methods

Subjects

Thirty six consecutive patients with confirmed COPD[24] and 14 current or ex-smokers were recruited from primary and secondary care and studied. All had participated in a study of arterial stiffness.[11] Subjects were excluded from the study if they were receiving long-term oxygen therapy or maintenance oral corticosteroids, or had known heart disease, malignancy, cor pulmonale or any other inflammatory or metabolic condition. Twenty patients had a negative Weber protocol treadmill exercise test. A further three had a recent normal coronary angiogram and Bruce protocol exercise test. Nine refusing an exercise test had a normal resting ECG. Of those completing an exercise test the mean duration was 7.5 min, seven achieving their maximal predicted heart rate. Exercise was stopped by breathlessness with no chest discomfort or ECG evidence of ischaemia: horizontal or down-sloping ST segment depression $\geq$ 1 mm. The study had Local Research Ethics Committee approval and all subjects gave written, informed consent.

Body composition, lung function and questionnaires

Height and weight were determined barefoot in light clothing and body mass index (BMI, kg/m^2) derived. Whole body fat free mass (FFM) was determined by Dual energy X-ray Absorptiometry (Hologic Discovery, Bedford, MA) and expressed as a height squared ratio to give whole body FFM index (FFMI). Similarly, the sum of lower limb FFM was expressed as a height^2 related index. A low whole body FFMI was defined as less than the lower 5th percentile of a cohort of gender-matched control subjects.[3] Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were determined by spirometry and the FEV_1/FVC ratio and FEV_1 and FVC % predicted values calculated.[24] Pulmonary diffusion capacity was determined by the single breath-hold carbon monoxide transfer factor corrected for alveolar volume (K_{CO}) in the patients (Pulmolab 501 system, Morgan Medical, Kent, UK). Arterialized ear lobe blood gases were determined at rest. All subjects completed an Epworth sleepiness score questionnaire to exclude obstructive sleep apnoea syndrome. The median score was 4, range 0—9.

Cardiovascular testing

Subjects were studied after an overnight fast and 6 h abstinence from caffeine, tobacco, inhaled short-acting β_2 agonist and antihypertensive medication.

Echocardiographic study

Echocardiography was performed blind by one operator (JE), using a Vivid 7 ultrasound system (GE, Horten, Norway). Annular velocities were measured in real time using pulsed wave tissue Doppler, while myocardial wall velocities and derived strain and strain rate curves were measured offline using dedicated software (EchoPAC, GE, Horten, Norway). Regional myocardial function was measured at the basal portion of the RV free wall, and at the basal portion of all 6 LV walls and averaged. All variables were the average of measurements in three consecutive cardiac cycles. Dimensions of the LV and RV were determined from M-mode recordings in the parasternal long-axis view. LV mass was calculated using the cubed formula. Ejection fraction and mean pulmonary arterial pressure were estimated using Simpson's biplane method and measurement of tricuspid regurgitant velocity respectively (Table 1).[25–28] Further details of individual echocardiographic parameters, their measurement and derivation of variables are given in the online methods supplement. A summary of all echo parameters and their relationship to cardiac function is presented in Table 1.

Intra-observer variability of TDE measurements was assessed by re-analysing a number of offline parameters in 10 randomly selected subjects. Intra-observer variability was calculated using Bland–Altman analysis and was <12% for all measurements.

Arterial stiffness

Peripheral blood pressure, pulse wave analysis and carotid-femoral (aortic) pulse wave velocity (PWV) were determined.[11,29] Further details of these measurements are available in the online methods supplement.

Inflammatory mediators and protein breakdown

Venous blood was collected for fasting glucose, lipids, interleukin (IL)-6 and tumour necrosis factor (TNF)-α soluble receptors (sr) 1 and 2.[3,11] A 10 ml second void urine sample was collected for measurement of pseudouridine (PSU) and creatinine by high performance liquid chromatography. The PSU concentration was expressed as a ratio to creatinine to correct for dilution.

Table 1 Echocardiographic indices determined in this study.

	LV	RV
Systolic		
	Ejection fraction	Peak tricuspid annular systolic velocity
	Peak mitral annular systolic velocity	Peak systolic velocity
	Peak systolic velocity	Peak systolic strain
	Peak systolic strain	Peak systolic strain rate
	Peak systolic strain rate	Isovolumic acceleration
Diastolic		
	Isovolumic relaxation time (IVRT)	Estimated pulmonary arterial pressure
	Mitral E/A	Pulmonary acceleration time
	E/E_A	Tei index
		Myocardial relaxation time

Statistical analysis

A formal sample size calculation was performed prior to the commencement of the study and was based on the results of a similar study in patients with cystic fibrosis.[30] Data were analysed with the Statistical Package for the Social Sciences (SPSS, Chicago, IL), version 12.0. Positively skewed data were Log_{10} transformed. Analyses included the χ^2 test, independent *t* test, Pearson's correlations, one way analysis of variance with Post hoc *Tukey* analysis and stepwise multiple regression analysis. A $p < 0.05$ was considered significant.

Results

Subject characteristics

Patients and controls were similar for age, gender, height, BMI, FFMI, lipid profile and fasting glucose (Table 2). Hypertension was present in 33% of patients and 14% of controls, $p = 0.25$. Statin use was similar between groups and no subjects were taking beta blockers. All patients received an inhaled short-acting β_2 agonist bronchodilator; 15 (42%) a long-acting β_2 agonist; 19 (53%) an anticholinergic bronchodilator; and 15 (42%) an inhaled

Table 2 Subject characteristics.

	Patients ($n = 36$)	Controls ($n = 14$)
Age (years)	66.5 ± 8.9	67.0 ± 8.8
Gender	19M, 17F	9M, 5F
Height (cm)	166 ± 7	169 ± 6
BMI (kg/m^2)	27.3 ± 4.9	26.9 ± 3.2
Whole body FFMI (kg/m^2)	17.2 ± 2.2	18.1 ± 2.1
Lower limb FFMI (kg/m^2)	5.2 ± 0.8*	5.8 ± 0.9
PSU (μmol/mmol creatinine)	34.7 ± 1.3	28.8 ± 1.2
LDL cholesterol (mmol/L)	3.64 ± 0.92	3.26 ± 0.71
Fasting glucose (mmol/L)	5.31 ± 0.5	5.56 ± 0.51
Smoking pack-year history	49.9 ± 15.6‡	16.4 ± 11.1
Serum IL-6 (pg/ml)[a]	2.14 ± 1.6†	1.29 ± 1.5
TNF-α sr1 (pg/ml)[a]	1380 ± 1.4	1259 ± 1.3
TNF-α sr2 (pg/ml)[a]	2399 ± 1.4	2188 ± 1.3
% Predicted FEV_1	56.9 ± 20.6‡	103.6 ± 15.2
% Predicted FVC	81.7 ± 23.5‡	104.6 ± 12.1
FEV_1/FVC %	53.8 ± 10.9‡	78.2 ± 4.6

Data are presented as mean ± standard deviation unless stated otherwise.
*$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ in comparison with control subjects.
Definition of abbreviations: BMI, body mass index; FFMI, fat free mass index; LDL, low density lipoprotein; IL-6, interleukin 6; TNF-α sr, tumour necrosis factor α soluble receptor; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.
[a] Geometric mean.

corticosteroid. More patients, 16, were current smokers than controls, 2 ($p < 0.01$), and pack-year exposure was greater than controls ($p < 0.01$). The median (range) arterial PaO_2 for the patients was 70 (57–88) mmHg.

Left ventricular structure and function

Mean LV mass, posterior wall thickness and ejection fraction were similar in patients and controls (Table 3). Compared with controls, patients had impaired longitudinal and regional systolic function with a reduced mean mitral annular peak systolic velocity ($p < 0.05$), average LV strain ($p < 0.01$) and peak systolic strain rate ($p < 0.001$) (Fig. 1a and b) (Table 3). Patients had diastolic dysfunction with a longer IVRT and a greater E/E_A (both $p < 0.01$).

Aortic stiffness and left ventricular function

While peripheral and central blood pressure was similar between patients and controls, aortic PWV was 22% greater in patients, $p < 0.001$. Heart rate ($p < 0.001$) and augmentation index (AIx) ($p < 0.05$) were also greater in patients (Table 3). In patients, aortic PWV was related to LV diastolic function; E/E_A ($r = 0.55$, $p < 0.01$); mitral E/A ($r = -0.38$, $p < 0.05$); mitral annular e/a ($r = -0.45$, $p < 0.01$); and IVRT ($r = -0.46$, $p < 0.01$), but not to any measures of systolic function. AIx was unrelated to systolic or diastolic function.

Table 3 Left ventricular function and arterial stiffness.

	Patients ($n = 36$)	Controls ($n = 14$)
Resting heart rate (bpm)	$75.4 \pm 8.8^{\ddagger}$	66.9 ± 10.6
LV mass* (g)	186.2 ± 1.41	190.0 ± 1.26
LV mass/BSA (g/m^2)	104.5 ± 27.7	103.8 ± 24.5
LV mass/FFMI	4.1 ± 0.9	3.8 ± 0.8
Mitral E/A	0.8 ± 0.2	0.9 ± 0.1
IVRT (ms)	$125.0 \pm 15.2^{\dagger}$	98.2 ± 21.1
Mitral annular relaxation (e/a)	0.8 ± 0.4	0.9 ± 0.3
E/E_A	$10.7 \pm 2.6^{\dagger}$	7.9 ± 1.6
Fractional shortening (%)	37 ± 5*	42 ± 6
Ejection fraction (%)	63 ± 4	67 ± 6
LV peak systolic velocity (cm/s)	5.5 ± 0.9	5.8 ± 0.6
LV systolic strain (%)	$-18.2 \pm 2.8^{\dagger}$	-21.0 ± 2.5
LV systolic strain rate (s^{-1})	$-1.3 \pm 0.2^{\ddagger}$	-1.7 ± 0.2
Lateral mitral annular peak systolic velocity (cm/s)	8.3 ± 2.0*	9.7 ± 1.4
Mean arterial pressure (mmHg)	106.5 ± 11.1	103.1 ± 6.2
AIx (%)	32.5 ± 8.6*	26.0 ± 5.4
Aortic PWV (m/s)	$11.5 \pm 2.9^{\ddagger}$	9.45 ± 1.3

Data are presented as mean ± standard deviation.
*$p < 0.05$, $^{\dagger}p < 0.01$, $^{\ddagger}p < 0.001$ in comparison with control subjects.
Definition of abbreviations: bpm, beats per minute; BSA, body surface area; AIx, augmentation index; PWV, pulse wave velocity; IVRT, isovolumetric relaxation time; LV, left ventricular.

Right ventricular structure and function

The RV free wall thickness was 31% greater in patients than controls, $p < 0.01$ (Table 4). Impaired longitudinal and global systolic function occurred in patients, who had a lower mean tricuspid annular peak systolic velocity ($p < 0.001$) and a greater Tei index ($p < 0.001$). Patients also had regional systolic dysfunction with lower basal peak systolic velocity ($p < 0.01$), strain ($p < 0.001$), peak systolic strain rate ($p < 0.001$) (Fig. 1a and b), and isovolumic acceleration ($p < 0.01$).

Indicators of raised pulmonary arterial pressure

Estimated mean pulmonary arterial pressure was similar between subject groups, but could not be determined in all subjects by the regurgitant tricuspid jet. Only one patient had a peak systolic pressure of >35 mmHg. However, pulmonary arterial hypertension was indicated by a greater Tei index, a longer basal free wall myocardial relaxation time ($p < 0.001$) and a shorter pulmonary acceleration time ($p < 0.01$) in the patients.

Severity of COPD and cardiovascular function

Patient subgroups were compared based on the severity of airways obstruction: $FEV_1 > 50\%$ predicted (GOLD I and II, $n = 20$) and $FEV_1 < 50\%$ predicted (GOLD III and IV, $n = 16$). Both subgroups were similar for age and gender. LV systolic dysfunction was present even in those with $FEV_1 > 50\%$ predicted, with a lower strain ($p = 0.01$), peak systolic strain rate ($p < 0.001$) and a lower mean mitral annular peak systolic velocity than controls (both $p < 0.05$). Both patient subgroups had LV diastolic dysfunction with a prolonged IVRT compared with controls (both $p < 0.01$).

Right ventricular dysfunction was also present in patients with milder lung disease, with a lower mean free wall peak systolic velocity ($p < 0.05$), strain ($p < 0.05$) and strain rate ($p < 0.01$) (Fig. 1a and b), and a lower mean tricuspid annular peak systolic velocity ($p = 0.001$) than in controls. The Tei index was different between all groups.

The FEV_1 was related to indices of pulmonary hypertension: pulmonary acceleration time ($r = 0.35$, $p < 0.05$); RV free wall thickness ($r = -0.37$, $p < 0.05$) and myocardial relaxation time ($r = -0.41$, $p < 0.05$) and Tei index ($r = -0.50$, $p < 0.01$). K_{CO} was related to RV free wall thickness ($r = -0.40$, $p < 0.05$) and IVRT ($r = -0.40$, $p < 0.05$). Arterial oxygen tension was also related to RV free wall thickness ($r = -0.33$, $p < 0.05$), and myocardial relaxation time ($r = -0.35$, $p < 0.05$).

Body composition and protein breakdown

Whole body FFM and FFMI were similar between groups, but lower limb FFMI was less in patients than controls, $p < 0.05$, and PSU excretion was greater in patients than controls, $p < 0.05$ (Table 2). Patients were sub-grouped as normal or low whole body FFMI, the latter for males <17.2 kg/m^2 and <13.7 kg/m^2 for females. Nine patients and one control subject had a low FFMI. The patient subgroups were similar for age, gender and FEV_1. LV mass ($p < 0.01$), peak systolic

Table 4 Right ventricular function and pulmonary arterial pressure.

	Patients ($n = 36$)	Controls ($n = 14$)
RV free wall thickness in diastole (cm)	$0.59 \pm 0.14^{\dagger}$	0.45 ± 0.06
RV internal dimension in diastole (cm)	2.5 ± 0.5	2.5 ± 0.5
Estimated pulmonary arterial systolic pressure (mmHg)	22.9 ± 2.1 ($n = 15$)	20.3 ± 3.2 ($n = 6$)
Pulmonary acceleration time (ms)	$188.7 \pm 27.0^{\dagger}$	216.9 ± 27.9
Tei index	$0.10 \pm 0.05^{\ddagger}$	0.07 ± 0.03
Lateral tricuspid annulus peak velocity (cm/s)	$12.0 \pm 1.9^{\ddagger}$	14.2 ± 1.6
Basal RV free wall		
Peak systolic velocity (cm/s)	9.2 ± 1.9*	10.8 ± 1.8
Myocardial relaxation time (ms)	$47.9 \pm 33.7^{\ddagger}$	12.6 ± 16.6
Strain (%)	$-18.6 \pm 5.4^{\ddagger}$	-24.3 ± 2.6
Peak systolic strain rate (s^{-1})	$-1.4 \pm 0.4^{\ddagger}$	-1.8 ± 0.4
Isovolumic acceleration (cm/s^2)	$1.6 \pm 0.6^{\dagger}$	2.3 ± 0.6

Data are presented as mean ± standard deviation.
*$p < 0.05$, $^{\dagger}p < 0.01$, $^{\ddagger}p < 0.001$ in comparison with control subjects.

velocity and strain (both $p < 0.01$), were less, and IVRT longer ($p < 0.05$) in the patients with a low whole body FFMI (Table 5). A low FFMI was associated with a longer mean RV myocardial relaxation time ($p < 0.01$) and a greater Tei index (both $p < 0.05$) (Table 5). Low FFMI patients had lower mean PaO_2 levels ($p < 0.05$) compared with normal FFMI patients.

Inflammatory mediators

Circulating IL-6 was greater in patients, while TNF-α sr1 and sr2 levels were similar (Table 2). In patients, Log_{10} IL-6 was related to pulmonary acceleration time ($r = -0.33$, $p < 0.05$); average LV strain ($r = -0.32$, $p < 0.05$) and mitral annular e/a ($r = -0.35$, $p < 0.05$). There were no relationships between the circulating IL-6, TNF-α sr 1 or 2 and total FFMI, PSU and LV mass.

Multivariate analysis

Predictors of LV systolic and diastolic function in the patients were determined by multivariate analysis with LV strain and IVRT respectively as dependent variables and age, FEV_1 % predicted, Log_{10} IL-6, peripheral mean arterial pressure (MAP), pack years smoked, whole body FFMI and aortic PWV as independent variables. Whole body FFMI was the only predictor of LV strain ($r^2 = 0.22$, $p < 0.01$), while aortic PWV was the only predictor of IVRT ($r^2 = 0.22$, $p < 0.01$). For predictors of global RV function and surrogate indices of pulmonary arterial pressure the same independent variables were used in addition to PaO_2, and % predicted FEV_1 was the only predictor of both RV Tei index ($r^2 = 0.23$, $p < 0.01$) and basal free wall myocardial relaxation time ($r^2 = 0.14$, $p < 0.05$).

A similar analysis for LV mass as the dependent variable, with age, gender, MAP, FEV_1 % predicted, Log_{10} IL-6, Log_{10} PSU, PaO_2 and total body FFMI as independent variables, revealed that whole body FFMI (adjusted $r^2 = 0.56$, $p < 0.01$) and PSU (adjusted $r^2 = 0.06$, $p < 0.05$) were the only predictors. Substituting whole body FFMI with lower limb FFMI in the same analysis revealed only the lower limb FFMI (adjusted $r^2 = 0.48$, $p < 0.01$) was a predictive variable.

Subjects without hypertension

A subgroup analysis excluding subjects with hypertension compared myocardial function in patients ($n = 24$) and

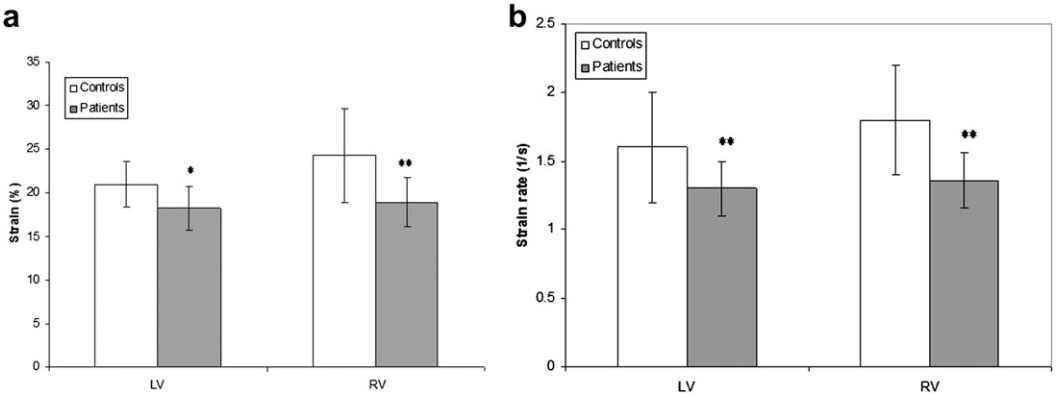

Figure 1 Left and right ventricular strain (a) and strain rate (b) in patients and controls. *$p < 0.01$,**$p < 0.001$. Error bars represent 1 standard deviation. *Open column* represents controls; *grey column* represents patients; □ controls; ■ patients.

Table 5 Comparisons between patients with a low or normal fat free mass index.

	Low FFMI ($n = 9$)	Normal FFMI ($n = 27$)
Log_{10} PSU (μmol/mmol creatinine)	38.1 ± 1.27	33.6 ± 1.31
LV mass (g)	159.0 ± 50.0*	209.6 ± 65.8
LV peak systolic velocity (cm/s)	$5.25 \pm 0.84^{\dagger}$	6.13 ± 0.79
LV strain (%)	$15.9 \pm 1.1^{\dagger}$	18.3 ± 2.0
IVRT (ms)	135.2 ± 16.0*	123.5 ± 12.5
RV myocardial relaxation time (ms)	$75.1 \pm 35.9^{\dagger}$	38.8 ± 28.1
Tei index	0.17 ± 0.06*	0.13 ± 0.05
PaO_2 (mmHg)	65.4 ± 6.7*	71.5 ± 6.9

Data are presented as mean ± standard deviation.
*$p < 0.05$, $^{\dagger}p < 0.01$ in comparison with normal FFMI subjects.

control subjects ($n = 12$). Similar to whole group analysis, patients with COPD had evidence of regional systolic LV dysfunction, LV diastolic dysfunction, RV systolic dysfunction and evidence of raised pulmonary arterial pressure.

Discussion

Sub-clinical left ventricular (LV) and right ventricular (RV) systolic and diastolic dysfunction was present in patients with COPD, free of overt cardiovascular disease, when compared with age and gender-matched smoking controls. The presence of LV and RV dysfunction in patients with mild severity airflow limitation suggests that cardiac complications may start to develop from early in the progress of lung disease and may remain sub-clinical for a long period. Both LV and RV dysfunction were associated with increases in their afterload due to increased aortic stiffness and raised pulmonary arterial pressure respectively.

Although LV ejection fraction was not different between patients and controls, other validated measures such as LV strain, strain rate and mitral annular peak systolic velocity were reduced in our patients indicating potential loss of regional LV contractility and impaired longitudinal LV systolic function. A number of animal and human studies have demonstrated that strain and strain rate reflect regional left ventricular function, while mitral annular peak systolic velocity has been shown to correlate with radionuclide ejection fraction.[25,31,32] LV systolic dysfunction in our patients was related to the severity of airways obstruction, FFMI and IL-6, though only FFMI was predictive. This suggests impairment is linked to the inflammatory-catabolic state in COPD, an interpretation supported by the LV mass also being predicted by whole body FFMI and lower limb FFMI, and to a lesser degree by PSU excretion, an indicator of protein breakdown in COPD.[3] This catabolic state is analogous to that reported in CHF,[24] and in our patients the catabolic drive appeared to offset any stimulus to LV hypertrophy in response to increased arterial stiffness.

Our findings of diastolic dysfunction in patients with COPD, indicated by an increased IVRT and E/E_A, are supported by two recent studies.[33,34] LV diastolic dysfunction in patients with COPD may be due to abnormalities in LV pre-load and/or afterload. Chest wall hyperinflation secondary to emphysema, may affect LV diastolic function by impairing LV filling and pre-load. This interpretation is supported by the inverse relationship between K_{CO} and IVRT. However, IVRT was only predicted by aortic PWV in an analysis including other accepted risk factors, which suggests a possible causal mechanism.[15,35,36] The earlier return of the reflected arterial wave augments aortic systolic pressure increasing LV afterload, while the concomitant reduction of aortic diastolic blood pressure may reduce coronary perfusion leading to sub-endocardial ischaemia. Both of these effects lead to myocardial fibrosis with impaired myocardial relaxation.[29] Thus, our patients are likely to have ventricular–arterial stiffening with impaired systolic and diastolic function in the absence of overt cardiovascular disease.[37] In this context our findings suggest a possible potential mechanism underlying the excess risk of coronary heart disease and CHF in COPD and possibly the relationship between airways obstruction, arterial stiffness and cardiovascular disease in the general population.[7,10,38–41]

Impaired RV systolic function, and in particular, reduced contractility as indicated by a lower free wall strain, strain rate and isovolumetric acceleration was present in the patients including those with even mild disease, when compared with controls.[12,13,27,42,43] None of our patients had clinical evidence of cor pulmonale and estimation of pulmonary arterial pressure using the tricuspid regurgitant jet did not separate patient and control groups; being quantifiable in less than half our subjects with only one with a pressure >35 mmHg. However, changes in surrogate indices of pulmonary arterial hypertension, including RV free wall myocardial relaxation time,[44] pulmonary acceleration time,[45] and Tei index,[46] indicated RV functional changes consistent with a degree of increased pulmonary vascular resistance and increased afterload in patients with both mild and severe lung disease. This confirms the findings of RV dysfunction without clinical evidence of cor pulmonale in patients with COPD where such features were mainly associated with pressures >35 mmHg, though, similar to our study, systolic strain and strain rate reductions were present in patients with pressures <35 mmHg.[12] The relationship of RV dysfunction and surrogate markers of pulmonary artery pressure to FEV_1, PaO_2 and K_{CO} was expected and confirms previously reported relationships.[12] The presence of sub-clinical RV dysfunction and indirect evidence of increased pulmonary arterial resistance in both mild and severe airways obstruction supports the early occurrence of pulmonary vascular changes and RV impairment without evidence of overt pulmonary hypertension in COPD. Sub-clinical RV dysfunction was reported to be related to the severity of lung disease and chronic inflammation in adults with cystic fibrosis free of cor pulmonale and in diabetes mellitus and rheumatoid arthritis.[30,47,48] While diagnosing cor pulmonale has negative prognostic implications,[6] the significance of sub-clinical RV dysfunction is currently unknown. Use of TDE to quantify RV function and pulmonary artery pressure may have potential in longitudinal studies of the natural history of cor pulmonale and possibly in therapeutic trials.

Limitations

The differences in tobacco exposure between patient and control groups are a potential confounder, hence pack-year exposure was included in our regression analysis. Subjects were asked to refrain from smoking 6 h before testing since the acute effects of smoking include an increase in aortic PWV and impairment of LV diastolic function.[49,50] Inclusion of subjects with hypertension is also open to criticism, so MAP was included in regression analysis and there was no difference in mean blood pressure indices between groups. In addition, a subgroup analysis excluding subjects with hypertension revealed similar results. We accept that the cross sectional nature and relatively low subject numbers in our study do not allow direct relationships between COPD and cardiac function to be inferred. However, our study has demonstrated strong associations which should be explored further.

Conclusions

This study in clinically stable patients with a wide range of severity of airways disease provides new evidence of subclinical LV and RV dysfunction and suggests cardiovascular co-morbidities may begin early in COPD and are often occult. Left ventricular diastolic dysfunction was related to arterial stiffness, indicating ventricular—arterial stiffening, while RV dysfunction was related to the severity of airways obstruction.

Acknowledgements

The authors would like to thank Dr Paul Temblett for his help in the design of the study.

Conflict of interests

None declared.

Funding sources

RS was a Clinical Research Fellow of the Cardiff and Vale NHS Hospital Trust. Other funding received from Glaxo Smith Kline Global.

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