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Clinical Research

T1 Measurements for Detection of Expansion of the Myocardial Extracellular Volume in Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: We aimed to assess whether chronic obstructive pulmonary disease (COPD) is associated with expansion of the myocardial extracellular volume (ECV) using T1 measurements.

Methods: Adult COPD patients Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage 2 or higher and free of known cardiovascular disease were recruited. All study patients underwent measures of pulmonary function, 6-minute walk test, serum measures of inflammation, overnight polysomnography, and a contrast cardiac magnetic resonance study.

Results: Eight patients with COPD were compared with 8 healthy control subjects. The mean predicted forced expiratory volume at 1 second of COPD subjects was 68%. Compared with control subjects, patients had normal left ventricular (LV) and right ventricular size, mass, and function. However, compared with control subjects, the LV remodelling index (median, 0.87; interquartile range [IQR], 0.71–1.14; vs median, 0.62; IQR, 0.60–0.77; $P = 0.03$) and active left atrial emptying fraction was increased (median, 46; IQR, 41–49; vs median, 38; IQR, 33–43; $P = 0.005$), and passive left atrial emptying fraction was reduced (median, 24; IQR, 20–30; vs median, 44; IQR, 31–51;

RÉSUMÉ

Introduction : Notre but était d'évaluer si la maladie pulmonaire obstructive chronique (MPOC) est associée à l'expansion du volume extracellulaire (VEC) myocardique en utilisant les mesures T1.

Méthodes : Des patients adultes souffrant d'une MPOC au stade 2 ou plus selon la classification GOLD (Global Initiative for Chronic Obstructive Lung Disease) et n'ayant pas de maladie cardiovasculaire connue ont été recrutés. Tous les patients de l'étude ont subi des mesures fonctionnelles pulmonaires, le test de marche de 6 minutes, des mesures sériques de l'inflammation, une polysomnographie nocturne et une étude d'imagerie par résonance magnétique cardiaque à l'aide d'un produit de contraste.

Résultats : Huit (8) patients souffrant d'une MPOC ont été comparés à 8 sujets témoins en santé. Le volume expiratoire maximal prédit moyen par seconde des sujets souffrant d'une MPOC était de 68 %. Comparativement aux sujets témoins, les patients avaient une taille, une masse et une fonction normales du ventricule gauche (VG) et du ventricule droit. Cependant, comparativement aux sujets témoins, l'indice de remodelage VG (médian, 0,87; intervalle interquartile [IIQ], 0,43; vs médian, 0,62; IIQ, 0,17; $P = 0,03$) et la fraction de vidange active de

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See page 1674 for disclosure information.

Cardiovascular morbidity and mortality among patients with chronic obstructive pulmonary disease (COPD) is high,^{1–3} but the mechanisms are unknown. Myocardial fibrosis is a marker of increased risk among broad groups of patients with cardiovascular disease^{4,5} and is confirmed pathologically in patients with advanced lung disease.⁶ Cardiac magnetic resonance (CMR) with the additive contrast technique of late

$P = 0.007$). The ECV was increased in patients with COPD (median, 0.32; IQR, 0.05; vs median, 0.27; IQR, 0.05; $P = 0.001$). The ECV showed a strong positive association with LV remodelling ($r = 0.72$; $P = 0.04$) and an inverse association with the 6-minute walk duration ($r = -0.79$; $P = 0.02$) and passive left atrial emptying fraction ($r = -0.68$; $P = 0.003$).

Conclusions: Expansion of the ECV, suggestive of diffuse myocardial fibrosis, is present in COPD and is associated with LV remodelling, and reduced left atrial function and exercise capacity.

gadolinium enhancement (LGE) is the gold-standard technique for the detection of replacement myocardial fibrosis.⁷ However, among patients with COPD, LGE is not detected,⁸ likely because LGE-based CMR measures for detection of myocardial fibrosis underestimate fibrosis when the entire myocardium is diffusely involved.⁹ Determination of the myocardial extracellular volume (ECV) using T1 measurements is a robust method for quantifying diffuse myocardial fibrosis.¹⁰⁻¹² The ECV using CMR has been validated against histological measures of fibrosis,^{10,11} is associated with measures of myocardial function,¹³ and is an independent predictor of mortality among broad populations with cardiovascular disease.¹⁴ We hypothesized that an expanded ECV would provide this marker of increased cardiovascular risk in patients with COPD. To design a definitive study, we first performed a pilot study in which we measured the ECV in a small, well characterized cohort of patients with COPD.

Methods

Study population

The study was approved by the local institutional review board and all participants gave their written informed consent. This study was completed over a period of 6 months from January to June, 2011, at Brigham and Women's Hospital. Adult patients (≥ 18 years of age) with known COPD diagnosed by a pulmonologist (defined as Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage 2 or higher and ≥ 10 pack-years of smoking history) were screened. Patients with standard contraindications to CMR (eg, claustrophobia, ferromagnetic devices, etc), receiving positive airway pressure therapy, uncontrolled COPD, known cardiovascular disease, a clinical history of heart failure or reduced ejection fraction, hypertension, diabetes, and pregnant women were excluded. After a telephone screening, patients presented for a history and physical examination, pulmonary function tests, blood tests, overnight polysomnography, 6-minute walk test, and a CMR study the next morning. Pulmonary function tests, including lung volumes and diffusing capacity, were performed according to the guidelines of the American Thoracic Society.¹⁵ Lung function measures of specific interest included forced expiratory volume at 1 second (FEV1), the degree of hyperinflation (measured according to residual volume divided by the

oreillette gauche étaient augmentés (médian, 46; IIQ, 8; vs médian, 38; IIQ, 10; $P = 0,005$), et la fraction de vidange passive de l'oreillette gauche était réduite (médian, 24; IIQ, 10; vs médian, 44; IIQ, 20; $P = 0,007$). Le VEC était augmenté chez les patients souffrant d'une MPOC (médian, 0,32; IIQ, 0,05; vs médian, 0,27; IIQ, 0,05; $P = 0,001$). Le VEC montrait une association positive importante avec le remodelage du VG ($r = 0,72$; $P = 0,04$) et une association inverse avec la durée du test de marche de 6 minutes ($r = -0,79$; $P = 0,02$) et la fraction de vidange passive de l'oreillette gauche ($r = -0,68$; $P = 0,003$).

Conclusions : L'expansion du VEC, qui évoque une fibrose myocardique diffuse et qui est présente dans la MPOC et associée au remodelage du VG, réduisait la fonction auriculaire gauche et l'aptitude à l'effort.

total lung capacity), and the forced expired flow from 25% to 75%. Blood samples were collected for measurement of markers of inflammation (high sensitivity C-reactive protein and interleukin-6) and hematocrit and creatinine. All study subjects with COPD underwent a supervised in-laboratory polysomnography to exclude the coexistence of previously undiagnosed obstructive sleep apnea. Sleep studies were scored by an experienced, blinded sleep technologist according to standard criteria¹⁶ and patients with an apnea-hypopnea index ≥ 10 per hour were a priori excluded. These patients were included in a previous published study detailing cardiovascular structure among patients with the overlap syndrome.¹⁷ All COPD study participants also completed the Epworth Sleepiness Scale to assess daytime sleepiness¹⁸ and the Modified Medical Research Council (MMRC) score to assess dyspnea before the polysomnography.¹⁸ We recruited healthy volunteer control subjects using open enrollment with an institutional review board-approved research Web site (<http://clinicaltrials.partners.org/>).¹¹ We specifically excluded volunteers with chest pain on exertion, any active or previous history of heart disease, stroke, diabetes, malignancy, sleep apnea, hypertension, an irregular heart rhythm, or atrial fibrillation, or any form of kidney disease. Healthy volunteers underwent testing with a comprehensive questionnaire detailing medical and medication history, peak flow measurement, standard anthropometric data, measurement of blood pressure, pulse, serum creatinine, and hematocrit, followed by a full CMR study with contrast. Healthy volunteers underwent a history and a physical examination by a board-certified pulmonologist. Healthy volunteers did not undergo a sleep study, Epworth Sleepiness Scale, MMRC score, 6-minute walk test, full lung function testing, or polysomnography.

CMR

All images were acquired with electrocardiographic gating, breath-holding, and with the patient in a supine position as previously described.⁴ Subjects were imaged on a 3.0-T CMR system (Siemens, Erlangen, Germany). The CMR protocol consisted of cine steady-state free precession imaging for left ventricular (LV), right ventricular (RV) volumes, function, and mass. All parameters were indexed by dividing the value by body surface area.¹⁹ All patients underwent an LGE imaging protocol for replacement myocardial fibrosis. A segmented

inversion-recovery pulse sequence for LGE was used starting 10-15 minutes after cumulative 0.15-mmol/kg dose of gadolinium diethylenetriamine penta-acetic acid (DTPA) (Magnevist; Bayer HealthCare Pharmaceuticals Inc, Wayne, NJ). The LV and RV remodelling index, as indices of concentric remodelling,²⁰ were calculated by dividing the LV and RV mass by their respective end-diastolic volume.

Evaluation of pulmonary arterial pressures

Pulmonary hypertension has been reported in patients with COPD. To assess indirectly whether pulmonary hypertension was present in this cohort we measured RV mass index²¹ and, among patients with COPD, peak and average pulmonary arterial (PA) blood velocity,^{22,25} and PA size.²³ The RV mass index has been shown to correlate with invasive measured PA pressures, and peak and mean PA velocities are reduced in patients with pulmonary hypertension.²³ Flow imaging was performed perpendicular to the main pulmonary artery with a velocity-encoded gradient echo sequence and a typical upper velocity limit of 150 cm/s (with further increases if any signal aliasing). The following typical imaging parameters were applied: repetition time/echo time, 5.9-7.5/2.3-3.1 ms; number of averages, 3; slice thickness, 5 mm; in-plane resolution, 1.0-2.0 mm; reconstructed cardiac phases, 30; and temporal resolution, 30-60 ms. Values for pulmonary flow velocities were compared with those in published reports.²³

Left atrial function

Left atrial (LA) volumes were calculated using the area-length method from the 2- and the 4-chamber views as previously described.²⁴ LA volumes were measured at the end of ventricular systole (defined as the frame immediately before opening of the mitral leaflets; LA VOL_{max}), at the end of passive LV filling (defined as the frame immediately before LA contraction; LA VOL_{bac}), and at the end of ventricular diastole (LA VOL_{min}). LA volumes were indexed to body surface area. From the LA volumes the following parameters were calculated: LA passive function (LAPEF) = $(LA\ VOL_{max} - LA\ VOL_{bac}) \times 100\% / LA\ VOL_{max}$, and LA active emptying fraction = $(LA\ VOL_{bac} - LA\ VOL_{min}) \times 100\% / LA\ VOL_{bac}$.

ECV fraction

T1 measurements were performed using a Look-Locker sequence with a non-slice-selective adiabatic inversion pulse, followed by a gradient echo acquisition (slice thickness, 8 mm; repetition time (TR) > 3 heart rate intervals precontrast and 2 heart rate intervals after contrast).¹¹ The T1 sequence was performed in a single slice in the midventricle and was repeated in the same mid-LV short-axis slice once before and 3 additional times after the injection of gadolinium spanning a 20-30 minute period. For each Look-Locker sequence, the endo- and epicardial borders of the left ventricle were traced and divided into 6 standard segments, and segments were numbered 1-6 starting from the anterior RV insertion point and proceeding in a clockwise direction (MASS Research, Leiden University Medical Centre, The Netherlands). The slope of the linear relationship (the partition coefficient for gadolinium, λ_{Gd}) was calculated and an ECV for all 6 myocardial segments was quantified as reported previously.^{11,25} A global ECV for each patient or healthy volunteer

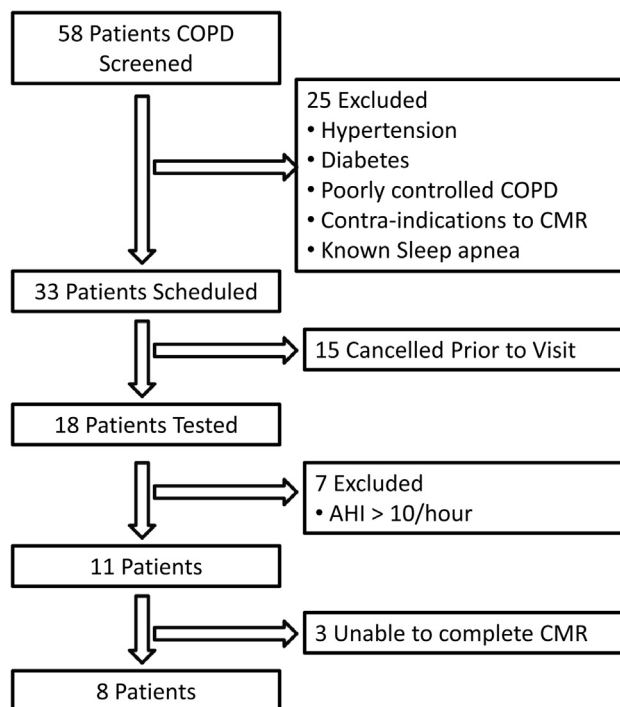


Figure 1. Study flow diagram. AH1, apnea-hypopnea index; CMR, cardiac magnetic resonance; COPD, chronic obstructive pulmonary disease.

was then calculated by averaging the 6 myocardial segmental values.

Statistical methods

Descriptive statistics are presented as medians with interquartile ranges (IQRs) for continuous variables and as numbers and percentages for categorical variables. Data were assessed for normality of distribution and homogeneity of variance. Because of the small sample size, continuous variables were analyzed using Mann-Whitney tests, and categorical variables were analyzed using the Fisher exact test. The relationships between 2 different parameters were evaluated using simple correlation analysis. Two sided *P* values of ≤ 0.05 were considered significant. All analyses were performed using GraphPad Prism 5 (GraphPad Software Inc, Chicago, IL) and SigmaPlot Version 11.0 (Systat Software Inc, San Jose, CA).

Results

From a consecutive series of 58 patients with known COPD, 25 subjects were excluded (exclusion criteria included hypertension, diabetes, poorly controlled COPD, known sleep apnea, and routine contraindications to the performance of CMR; Fig. 1). From this group, 33 patients were scheduled for study visits, of whom, 15 cancelled before the visit. The cohort of 18 patients underwent testing; 7 of these had previously undiagnosed sleep apnea and were excluded leaving the final study population of 11 patients. Of these 11 patients, all underwent a CMR study but 3 were unable to complete the CMR study, 2 because of claustrophobia and 1 because of

Table 1. Study subject characteristics

Variable	Healthy Control Subjects (n = 8)	COPD Subjects (n = 8)	P
Age, years	63 (56, 68)	60 (57, 68)	0.96
Female sex, n (%)	6 (86)	6 (86)	1.00
Body mass index	25.9 (23.1, 35.1)	26.6 (22.0, 29.1)	0.72
Body surface area, m ²	1.8 (1.7, 2.0)	1.8 (1.7, 1.9)	0.80
Heart rate, beats per minute	70 (59, 81)	67 (55, 68)	0.33
Systolic blood pressure, mm Hg	125 (121, 129)	128 (117, 129)	0.88
Diastolic blood pressure, mm Hg	74 (65, 79)	69 (68, 70)	0.38
Hematocrit, %	45 (39, 46)	44 (42, 46)	0.96

Results are expressed as median (lower quartile, upper quartile), unless otherwise specified. Body mass index calculated as weight (kg)/height (m²).

COPD, chronic obstructive pulmonary disease.

an inability to breath-hold. This process left a final study population of 8 patients. Healthy volunteer subjects for comparison were selected from a larger cohort of 32 healthy volunteers to age- and sex-match the 8 subjects with COPD recruited as part of this study. There was no significant difference in age, sex, body mass index, body surface area, heart rate, blood pressure, or hematocrit between COPD patients and controls (Table 1). All patients, from the cohort of healthy volunteers used in this study and the study subjects, self-identified as being Caucasian. The peak flow of the 8 healthy volunteers averaged 398 L/min for the female volunteers and 560 L/min for the male volunteers.

COPD severity

Patients with COPD had a median duration of diagnosis of 5.5 years (interquartile range, 3.75-6.5). The median duration of smoking in pack years was 40 (interquartile range, 19.4-75). All patients were using an inhaled bronchodilator at the time of the study, 3 patients (37.5%) were using inhaled steroids, no patient was using oral prednisone and no patient had required in-patient admission for an acute exacerbation of COPD in the 12-month calendar period before the study. The average predicted FEV1 was 65 ± 9%, average predicted forced vital capacity (FVC) was 84 ± 12%, FEV1/FVC was 0.6 ± 0.07, diffusing capacity of the lung for carbon

monoxide 11.9 ± 1.9 mmol CO per min/kPa, forced expiratory flow 25-75% (FEF25-75) was 37 ± 18%, and RV/total lung capacity (TLC) was 117 ± 29%. The average apnea-hypopnea index was 4.9 ± 1.5 events per hour, the oxygen desaturation index was 10.4 ± 4.4 events per hour, and the MMRC score was 1.38 ± 0.9. The 6-minute walk distance was 277 ± 27 m. The mean hs-CRP was 2.4 ± 2.1 mg/L and mean interleukin-6 was 5.3 ± 1.9 pg/mL.

CMR measures of cardiac size, function, and PA pressures

There was no difference in LA volume, LV volume, LV mass, or LV ejection fraction between patients with COPD compared with healthy control subjects (Table 2). The LV remodelling index was increased in patients with COPD compared with control subjects (median, 0.87 [IQR, 0.71-1.14] vs 0.62 [IQR, 0.60-0.77]; P = 0.03; Fig. 2). There was no difference in RV volumes, RV mass, or RV function between patients with COPD and healthy control subjects. The peak and mean PA blood flow velocities were preserved at 95 ± 15 cm/s and 15 ± 6 cm/s, respectively.²³ In comparison, the peak and mean velocities in a group of healthy control subjects were 84 ± 22 cm/s and 16 ± 5 cm/s, respectively.²³ The RV remodelling index was also similar between patients with COPD and control subjects (median 0.23 [IQR, 0.19-0.29] vs 0.23 [IQR, 0.16-0.25]; P = 0.72). No patient had replacement myocardial fibrosis detected using LGE imaging.

LA volumes and function

There was no difference in the maximum or minimal LA volumes between patients and control subjects (Table 2); however, LA volumes at the end of passive LV filling (LA VOL_{bac}) was increased in patients compared with control subjects (median, 26 [IQR, 23-29] vs 16 [IQR, 14-26]; P = 0.05). LAPEF was reduced (median, 24 [IQR, 20-30] vs 44 [IQR, 31-51]; P = 0.007), and LA active function (LA active emptying fraction; median, 46 [IQR, 41-49] vs 38

Table 2. Comparison of CMR measures between healthy control and COPD subjects

Variable	Healthy Control (n = 8)	COPD (n = 8)	P
Maximal LA volume index, mL/m ²	31 (27, 38)	36 (33, 38)	0.28
LA volume before atrial contraction, mL/m ²	16 (14, 26)	26 (23, 29)	0.05
Minimal LA volume index, mL/m ²	10 (9, 15)	15 (13, 16)	0.10
LA passive ejection fraction, %	44 (31, 51)	24 (20, 30)	0.007
LA contractile ejection fraction, %	38 (33, 43)	46 (41, 49)	0.005
Right atrial area index, cm ² /m ²	5.2 (4.2, 7.9)	7.2 (6.4, 11.1)	0.04
LV end-diastolic volume index, mL/m ²	66 (55, 81)	64 (56, 67)	0.57
LV end-systolic volume index, mL/m ²	25 (19, 33)	24 (21, 28)	0.96
LV ejection fraction, %	61 (58, 69)	63 (56, 66)	0.51
LV mass index, g/m ²	46 (39, 56)	55 (49, 63)	0.08
LV remodelling index, g/mL	0.62 (0.60, 0.77)	0.87 (0.71, 1.14)	0.03
RV end-diastolic volume index, mL/m ²	65 (56, 70)	71 (51, 85)	0.51
RV end-systolic volume index, mL/m ²	29 (25, 38)	32 (24, 43)	1.00
RV ejection fraction, %	54 (50, 60)	53 (51, 54)	0.57
RV mass index, g/m ²	13 (11, 16)	16 (14, 16)	0.28
RV remodelling index, g/mL	0.23 (0.16, 0.25)	0.23 (0.19, 0.29)	0.72
Extracellular volume	0.27 (0.25, 0.30)	0.32 (0.31, 0.36)	0.001

Results are expressed as median (lower quartile, upper quartile).

CMR, cardiac magnetic resonance; COPD, chronic obstructive pulmonary disease; LA, left atrial; LV, left ventricular; RV, right ventricular.

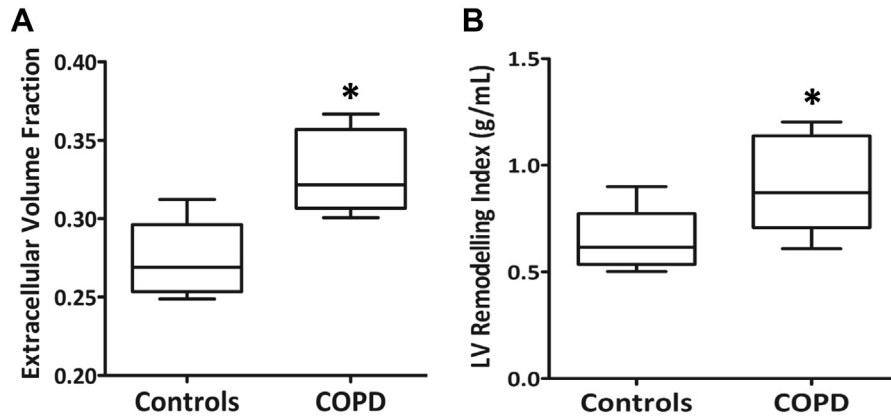


Figure 2. Comparison of the (A) extracellular volume fraction and (B) the left ventricular (LV) remodelling index between patients with chronic obstructive pulmonary disease (COPD) and healthy control subjects. * = $P < 0.05$.

[IQR, 33-43]; $P = 0.005$) was increased in patients with COPD compared with control subjects.

ECV fraction

The ECV was increased in patients with COPD compared with control subjects (median, 0.32 [IQR, 0.31-0.36] vs median, 0.27 [IQR, 0.25-0.30]; $P = 0.001$; Fig. 2). Among healthy control subjects there was no difference in the segmental ECV from the anterior segment through to the anteroseptal segment (0.27 ± 0.03 , 0.27 ± 0.03 , 0.28 ± 0.03 , 0.27 ± 0.02 , 0.28 ± 0.02 , and 0.27 ± 0.02 ; $P = 0.87$). Similarly, among patients with COPD, there was no difference in the segmental ECV values from the 6 different segments (0.33 ± 0.03 , 0.32 ± 0.02 , 0.32 ± 0.03 , 0.32 ± 0.02 , 0.35 ± 0.05 , and 0.34 ± 0.05 ; $P = 0.73$). Representative ECV measurements in a patient with COPD and a healthy control subject are shown in Figure 3. Among patients with COPD, there was no statistically significant association between the ECV and the duration of COPD ($r = 0.51$; $P = 0.20$), pack-years history ($r = 0.21$; $P = 0.61$), FEV1

($r = 0.04$; $P = 0.92$), FVC ($r = 0.08$; $P = 0.88$), FEV1/FVC ($r = -0.14$; $P = 0.76$) or the diffusing capacity of the lung for carbon monoxide ($r = 0.22$; $P = 0.62$). There was also no association between the ECV and serum measures of inflammation (ECV vs hs-CRP, $r = -0.09$; $P = 0.83$), and measures of RV size or function. Four of the subjects were active smokers and 4 were previous smokers. We did not find a difference in the ECV between current and active smokers (median, 0.33 [IQR, 0.31-0.36] vs 0.32 [IQR, 0.30-0.36]; $P = 1.00$). There was, however, a strong inverse association between ECV and the 6-minute walk distance ($r = -0.79$; $P = 0.02$) and LA passive emptying fraction (LAPEF, $r = -0.69$; $P = 0.003$), and a positive association between the ECV and the LV remodelling index ($r = 0.72$; $P = 0.04$).

Discussion

In this pilot study, we performed a contrast CMR study in patients with COPD. Our hypothesis was that patients with COPD free of overt cardiovascular disease would have imaging evidence of diffuse myocardial fibrosis. We found that the ECV, a noninvasive measure of diffuse myocardial fibrosis,

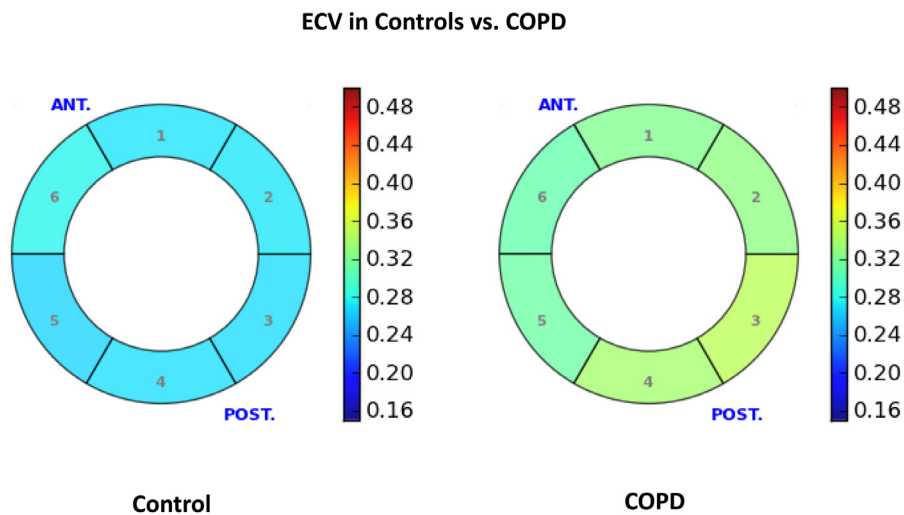


Figure 3. Representative bulls-eye comparison of the extracellular volume fraction (ECV) between a healthy control subject (average ECV, 0.27) and a patient with chronic obstructive pulmonary disease (COPD) (average ECV of 0.33). The figure shows a short-axis view of the midslice of the left ventricle with the ECV of each segment represented by colour using the colour chart to the right. ANT., anterior; POST., posterior.

was increased in patients with COPD. We found that an increased ECV was associated with a low 6-minute walk time, reduced LA function, and adverse LV remodelling.

We observed that an increased ECV had a strong association with reduced functional capacity, LA function, and adverse LV remodelling. The LV remodelling index provides an index of wall thickness to cavity size and is the equivalent of the echocardiogram-derived relative wall thickness.²⁰ In patients with COPD, the increase in the LV remodelling index represented a combination of a minimally increased LV wall thickness and mass, with a relative reduction in the volume of the LV cavity. As a result, the ratio of LV mass to end-diastolic volume increased. Concentric LV remodelling is associated with a reduction in systolic and diastolic function,^{26,27} and is an independent marker of increased risk in patients with and without cardiovascular disease.²⁸⁻³⁰ There was also a strong inverse association between the ECV and exercise duration. The 6-minute walk test is a robust measure of outcomes in patients with COPD.^{31,32} These findings of an association between the ECV and functional status is novel in adults, and is in agreement with a previous description in a pediatric population.³³ Finally, we found an inverse association between the ECV and passive LA function. We did not directly measure LV diastolic function, although it is known that LV diastolic function and LA passive ejection fraction are strongly related.^{34,35} The novel finding of a relationship between the ECV as a measure of myocardial fibrosis and LA function passive function, as a surrogate for LV diastolic function, appears reasonable based on published data.^{36,37}

Ultimately, we aim to test our hypothesis that an expanded ECV will provide a biomarker identifying patients with COPD that are at increased cardiovascular risk. The ECV has been validated as a noninvasive surrogate of myocardial fibrosis in animals and humans,^{10,11} and in patients with heart failure is associated with measures of diastolic function and atrial enlargement,¹³ and provides independent prognostic information.¹⁴ There are limited data related to testing for the presence of myocardial fibrosis in patients with COPD. Kohama and colleagues measured the extent of myocardial fibrosis in an autopsy study of a heterogeneous group of patients who died of advanced lung disease.⁶ They found that patients had increased myocardial fibrosis in the left ventricle, specifically, the septum of the left ventricle. There are limited noninvasive studies but Murphy and colleagues tested the prevalence of LGE, or replacement myocardial fibrosis, in a small population of patients with COPD.⁸ Similar to our study, none of the 25 patients with COPD in the previous study had LGE. However, despite the lack of LGE in our study, we found that patients had evidence of diffuse interstitial fibrosis. Although expansion of the ECV can occur because of pathological processes other than fibrosis and collagen, we believe that this explanation represents the most logical possibility in this cohort. We excluded patients with diabetes, making abnormal cross-linking of fibres unlikely, and our population had no clinical or imaging evidence of amyloid or sarcoid.

The causes of an increased ECV and myocardial fibrosis in this population are unclear. We cannot exclude secondary pulmonary hypertension.³⁸ However, we believe that the pulmonary pressures are unlikely to have been markedly increased for several reasons. First, our patients had relatively

preserved FEV1, and important pulmonary hypertension is uncommon in ambulatory COPD patients especially until the FEV1 decreases to < 50%.³⁹ Second, RV mass has been reported to correlate well with catheterization-derived mean pulmonary pressures. We found no significant difference in right ventricular mass index (RVMI). Third, peak and mean PA velocities, which are reduced in patients with pulmonary hypertension,²³ were preserved in this population. In our study, the FEV1 was 68% of predicted, in comparison to an FEV1 of 41% in the study of Vonk-Noordegraaf and colleagues⁴⁰ and a FEV1 of > 40% in the study of Hilde and colleagues.⁴¹ We also tested for occult sleep apnea because sleep apnea is a frequently underdiagnosed comorbidity in patients with COPD,⁴² and treatment of undiagnosed sleep apnea has been shown to reverse pulmonary hypertension,⁴³ and reduce COPD exacerbation-related hospitalizations and mortality.⁴⁴ However, none of our patients included in this study had sleep apnea using a threshold of apnea hypopnea index of < 10 events per hour. We therefore believe that the most likely mechanism for an increase in myocardial fibrosis involves the association between COPD, inspiratory intrathoracic pressures, and LV afterload.^{45,46} Patients with COPD can generate markedly negative pleural pressure on inspiration⁴⁷ (eg, during hyperinflation with auto-positive end expiratory pressure [PEEP]), and it is possible that these pressures might increase LV wall stress from an increased afterload and induce myocardial fibrosis.

Limitations

Our study has some limitations that merit discussion. This was a pilot study with a small number of participants, which limits some of the statistical interpretations. Our sample size would have limited the ability to detect difference in measures such as LV mass, RV mass, and RV remodelling index.⁴⁶ Further, we were unlikely to detect significant differences in descriptive variables between groups that might have led to bias in interpretation; however, qualitative assessment of the groups suggest that the COPD patients and control subjects were well-matched. We acknowledge that smoking among the COPD patients might have contributed to increased ECV; further studies are needed to clarify this issue. Our study included selected patients from a single medical centre, which could affect the generalizability of our findings. The study was approved by the local institutional review board and all testing and data recording were done prospectively and as part of the prespecified study protocol. This protocol did not include the performance of an echo and a right heart catheterization. We also did not perform a formal sleep study or full pulmonary function tests in our healthy volunteers. However, none of our volunteers were smokers, none had a history of pulmonary disease, they were of normal weight, had normal spirometry, and all underwent a thorough history and physical examination by a licensed pulmonologist making the probability for presence of occult pulmonary disease relatively low. A future area of research is to test methods for measurement of the ECV in the RV free wall. However, at present, we are unable to measure the ECV in a nonhypertrophied RV free wall because the spatial resolution is not sufficient. Finally, we did not test LV and RV systolic function beyond measures of

ejection fraction or test whether an expanded ECV was associated with subtle RV dysfunction.⁴¹

Conclusions

Patients with COPD without clinical heart failure have an increased ECV. This increase in the ECV in COPD is associated with measures of exercise capacity and adverse LV remodelling. The mechanism for this increase is not clear but is likely due to myocardial fibrosis. Further data through mechanistic research and clinical trials are required to determine if this preliminary finding can be replicated in larger studies, whether the increase in the ECV is associated with the risk for development of subsequent heart failure, and whether intervention based on this measure can reduce the risk for development of adverse clinical outcomes in this high-risk population.

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Disclosures

The authors have no conflicts of interest to disclose.

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