SUPPLEMENTARY MATERIAL

Title: **Effect of dynamic hyperinflation on cardiac response to exercise of patients with chronic obstructive pulmonary disease**

METHODS

Study subjects

Fifty-seven COPD patients were consecutively recruited from an academic medical center (Hospital Universitario La Paz, Madrid, Spain). Inclusion criteria were: clinical diagnosis of COPD more than six months earlier; postbronchodilator FEV_1/FVC <0.7 and <lower limit of normal, with FEV_1 <80% predicted; history of smoking >20 pack-years; stable condition at inclusion, with no infection or exacerbation for at least 2 months; and optimal medical therapy for at least 8 weeks with no change. Exclusion criteria were the existence of a previous diagnosis of asthma, interstitial lung disease, pleural or chest wall disease, heart failure, ischemic or valvular heart disease; previous treatment with inotropic or vasodilator drugs; use of long-term oxygen therapy; contraindication for performing cardiopulmonary exercise tests; and locomotor disorder or any other disabling disease for exercise. Medication was kept constant during the course of the study. As a control group, 25 healthy subjects were randomly selected from the reference group of our laboratory, trying to maintain a 1:2 ratio with COPD patients in sex, age (± 4 years), weight (± 5 Kg) and smoking status (current or former smokers). The study was approved by the La Paz Hospital Medical Ethics Committee (PI-513), and informed consent was given by all subjects.

1

Clinical and functional evaluation

For all subjects, body composition was evaluated using bioelectrical impedance analysis (Bodystat, Isle of Man, UK). Smoking habits were collected, and baseline dyspnea level was assessed by the modified Medical Research Council (mMRC) scale. Self-reported comorbidity was documented using the Charlson index, and quality of life was assessed using the validated Spanish version of the St. George's Respiratory Questionnaire (SGRQ). Moreover, the International Physical Activity Questionnaire (IPAQ) was used to evaluate the level of daily physical activity. Additionally, in COPD patients, GOLD risk group, BODE and ADO multidimensional indices, current treatment and COPD Assessment Test (CAT) score were also recorded.

Arterial blood gas values breathing room air were measured (ABL90 Flex, Radiometer, Bronshoj, Denmark). Spirometry was performed by means of a pneumotachograph, and static lung volumes were measured with a constant-volume body plethysmograph. Diffusing capacity for carbon monoxide was determined by the single-breath method (MasterLab Body, Viasys, Hoechberg, Germany), according to current recommendations.[1-3] As reference values, Global Lung Function Initiative (GLI)[4,5] equations were used for spirometric and diffusing capacity parameters, whereas European Coal and Steel Community[6] equations were used for lung volumes. The 6-min walk test was carried out in a 30 m corridor in accordance with the guidelines of the American Thoracic Society.[7] The longest distance of 2 tests was taken, separated by a minimum 30-minute interval.

Systemic and airway biomarkers

Prior to lung function tests, samples of plasma and exhaled breath condensate (EBC) were collected and immediately stored at -80°C. Approximately 2 mL of EBC were obtained after 10 min of relaxed tidal breathing using an EcoScreen condenser (Viasys). In plasma samples, we measured a panel of biomarkers related to inflammatory and immune response (interleukin [IL]-6, IL-8, IL-1β, IL-17A, tumor necrosis factor [TNF]-α, macrophage inflammatory protein [MIP]-1α and highly sensitivity C-reactive protein [hsCRP]), oxidative stress (8-isoprostane and glutathione peroxidase [GSX]-1), tissue damage/repair (galectin-3 and N-terminal procollagen III propeptide [PIIINP]) and cardiac involvement (N-terminal cerebral natriuretic propeptide [NT-proBNP], high-sensitivity cardiac troponin T [hs-cTnT] and homocysteine). As biomarkers of airway inflammation, concentrations of IL-1β, IL-6, IL-8 and TNF-α were determined in exhaled breath condensate. Table S1 details the measurement techniques, as well as the detection limits and intra-assay coefficient of variation of each biomarker.

Computed tomography technique and image analysis

CT examinations were performed without intravenous contrast injection using the same 16-row multidetector CT scanner (Somatom Emotion 16, Siemens, Erlangen, Germany) with the following parameters for both inspiratory and expiratory scans: slice width, 0.3 mm; reconstruction increment, 0.5 mm; collimation, 16x0.75 mm; pitch, 0.8; slice collimation, 0.6 mm; voltage, 120 kVp; reference tube current-time, 160 mAs; and rotation time, 0.6 s. All subjects were thoroughly coached in breathing techniques prior to the CT scan. They received standardized instructions for breath-holding at deep inspiration and end-tidal expiration during the spiral CT acquisition

from apex to base of the lung. Routine matrix clinical images were reconstructed with high-resolution B31f and B35f for inspiratory and expiratory CT scans.

Post-processing was performed in an independent reconstruction console (Leonardo, Siemens) using a semiautomatic analysis program (Syngo InSpace4D, Siemens) that performs a quantitative evaluation of the attenuation of lung parenchyma. Mean lung density (MLD) in Hounsfield units (HU), low attenuation value (LAV) as percentage of lung tissue with HU below −950, subrange 1 as percentage of lung tissue with attenuation values between -1000 and -951 HU and 15th percentile of HU (P15) were calculated on maximal inspiration and expiration.

Echocardiography

Transthoracic echocardiography at rest was performed in all subjects by an experienced echocardiographer based on the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (EACVI).[8] Further independent evaluation was performed offline.

Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular posterior wall thickness at end diastole (LVPW) and interventricular septal thickness at end diastole (IVS) were measured from the 2-dimensionally guided M-mode tracings, and left ventricle (LV) mass was calculated accordingly and adjusted for body surface area.[8] Left ventricular ejection fraction (LVEF) was calculated from LV end-systolic and end-diastolic volumes measured from the apical 4- and 2-chamber views, using the modified biplane Simpson method.[9] Left atrial area (LAA) was measured from apical four chamber view at the end systole, shortly before the mitral valve opens.

4

With standard transthoracic pulsed wave (PW)-Doppler echocardiography using the apical four-chamber view, the peak early-diastolic (E), atrial systolic (A) transmitral flow velocities, and deceleration time of the E wave (DT) were measured in accordance with the EACVI recommendations for the evaluation of LV diastolic function.[10] The evaluation of diastolic function was complemented by lateral mitral annular velocity measured by tissue Doppler imaging.[11] We calculated the E/e' ratio by dividing transmitral E peak by early peak diastolic velocity of the mitral annulus displacement (e') using the average of three consecutive Doppler signals. Diastolic dysfunction and LV filling pressure were staged according to current criteria.[12]

The right atrium (RA) area was measured in the apical four-chamber view at end-systole by tracing the RA blood-tissue interface.[11] Tricuspid annular plane systolic excursion (TAPSE) was calculated as index of right ventricle (RV) longitudinal systolic function by placing an M-mode cursor through the tricuspid annulus in a standard apical four-chamber window, and measuring the difference between end-diastolic and end-systolic amount of longitudinal motion of the annulus.[12,13] Pulmonary artery systolic pressure (PASP) was calculated by adding a value of RA pressure (RAP) as measured by inferior vena cava respiratory index to the systolic trans-tricuspid gradient (PASP = $4V^2$ + RAP, where V = maximal velocity of tricuspid regurgitation jet). PASP was assumed to equate the RVSP in the absence of pulmonic stenosis and/or right ventricular outflow tract obstruction.[14]

Exercise testing and cardiac response to exercise

After 30 min of rest, symptom-limited incremental cycle exercise tests were conducted on an electronically braked cycle ergometer (Ergobex, Bexen, Spain) following

standards of the ATS/ACCP statement,[15] as previously described.[16] Equipment was calibrated immediately before each test. The initial 2 min consisted of resting data collection followed by 1 min of unloaded cycling. Subsequently, workload was increased by 15 W/min until maximal symptom-limited exercise was achieved. Pedaling rates were maintained between 50 and 60 revolutions per minute. Expired gases and ventilation were measured on a metabolic cart that uses a pneumotachograph positioned at the mouth with O_2 and CO_2 analyzers (Oxycon Alpha, Viasys). This allowed for breath-by-breath measurements of oxygen consumption (VO_2), carbon dioxide production (VCO_2), minute ventilation (VE), respiratory rate (f), and tidal volume (VT). The continuous output of the automated system was recorded and displayed on an on-line PC computer. where all data were saved for later analysis. The system was calibrated to ensure an appropriate phase response. The predicted values of Jones and coworkers were used for the exercise measurements.[17] For all patients, heart rate, heart rhythm, blood pressure, and oxygen saturation were continuously monitored. In addition, full 12-lead electrocardiograms were monitored during each minute of exercise and recovery. Oxyhemoglobin saturation (SpO_2) was continuously monitored by a finger pulse oximeter (Oscar II, Datex, Helsinki, Finland). Peak work rate (Wpeak) was defined as the highest work rate that the subject was able to maintain for at least 30 s. Anaerobic threshold (AT) was estimated using the nadirs of ventilatory equivalents and the V-slope method; both methods were used concurrently looking for consistency.[15] If AT was clearly discernible using either of the noninvasive methods, this value was reported. When differences in AT were observed between both techniques, the average value was used. However, in situations in which

6

AT was not discernible using either method, the AT was categorized as indeterminate. The predicted values of Jones were used.[17]

Changes in operational lung volumes were evaluated from duplicate measurements of inspiratory capacity (IC) at rest and every 2 min during exercise (Oxycon Alpha).[18] If efforts appeared submaximal or if anticipatory changes in breathing pattern occurred immediately preceding a maneuver, then the IC was not accepted. EELV was calculated as total lung capacity (TLC) minus IC. To minimize the variability of isolated EELV measurements, we considered that the patient had developed DH when the slope of linear regression of the EELV as a function of time was higher than zero.[19] In addition, the difference between the last EELV measurement, near end-exercise, and the resting value was computed.

On a following day, to avoid the potentially confounding effects of peripheral muscle fatigue, patients performed other incremental cycle exercise tests to perform a non-invasive measurement of cardiac output by an inert gas rebreathing method (Innocor, Innovision, Odense, Denmark).[20] Previously, patients were instructed on the breathing technique and performed at least 1 practice measurement before each test. After 5 minutes at rest, exercise began at a workload of 0 W and increased 15 W each minute until symptom-limited maximal exercise was reached. Expired gas analysis was performed continuously throughout the test with the Innocor system, which uses an oxygen-enriched mixture of an inert soluble gas (0.5% nitrous oxide) and an inert insoluble gas (0.1% sulfur hexafluoride) from a 4-L prefilled anesthesia bag. Photoacoustic analyzers measured gas concentrations over a 5-breath interval. Tidal volume was progressively increased in the closed circuit to match the physiologic increase. The use of sulfur hexafluoride allowed us to measure the volume of the

lungs, valve, and rebreathing bag. Nitrous oxide concentration decreased during the rebreathing maneuver, with a rate proportional to pulmonary blood flow. Three to 4 respiratory cycles were needed to obtain nitrous oxide washout. Absence of pulmonary shunt was defined as arterial oxygen saturation >98% by pulse oximetry. SV and CO measurements were made at the end of the resting period, at 15 W, and at 45 W. Cardiac response to exercise was assessed through the $\Delta SV/\Delta VO_2$, $\Delta CO/\Delta VO_2$ and Δcardiac index (CI)/ΔVO_2 slopes, calculated by linear regression of the three measurements.

Statistical analysis

The sample size was estimated from a previous pilot study showing a SV/VO_2 slope of 11.81 ± 7.46 in healthy subjects.[21] To recognize as statistically significant a difference greater or equal to 6, accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 25 subjects are necessary in each group. Assuming that up to 70% of COPD patients develop DH, it would be necessary to recruit 57 COPD patients to obtain two comparable groups according the presence or absence of this disorder.

Normality in the distribution of the data for each variable was explored using skewness-kurtosis tests. Values are expressed as mean ± standard deviation, median and interquartile range or percentage, according their type and distribution. All statistical tests were two-sided. Comparisons between groups were performed with the Student's *t*, Mann-Whitney or chi-square tests. The relationships between variables were determined using Pearson's correlation. Significant contributors to cardiac response to exercise were then introduced in a stepwise multiple linear regression analysis to identify independent determinants of the SV/VO_2 slope. In the multiple linear regression analysis, predictor variables were retained only if their

addition significantly improved (P<0.05) the fraction of explained variability (r^2). Other

aspects explored included residual standard deviation, changes in the distribution of

the residuals and the homogeneity of the variance over the predictors. Statistical

significance was assumed for P<0.05. All analyses were performed using the Statistical

Package for the Social Sciences, version 1.0 software (SPSS Inc., Chicago, IL, USA).

REFERENCES

1. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardization of spirometry. Eur Respir J. 2005;26:319-38.

2. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardization of the measurement of lung volumes. Eur Respir J. 2005;26:511-22.

3. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CPM, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26:720-35.

4. Quanjer PhH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40:1324-43.

5. Stanojevic S, Graham BL, Cooper BG, Thompson BR, Carter KW, Francis RW, et al. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. Eur Respir J. 2017;50:1700010.

6. Quanjer PhH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault J-C. Lung volumes and forced ventilatory flows. Eur Respir J. 1993;6(suppl 16):5-40s.

7. ATS Statement: Guidelines for the six-Minute Walk Test. Am J Respir Crit Care Med. 2002; 166: 111-7.

8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16:233-70.

9. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18:1440-63.

10. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29:277-314.

11. Mitter SS, Shah SJ, Thomas JD. A test in context: E/A and E/e' to assess diastolic dysfunction and LV filling pressure. J Am Coll Cardiol. 2017;69:1451-64.

12. Hayashi S, Yamada H, Nishio S, Hotchi J, Bando M, Tagawa Y, et al. Age- and gender-specific changes of tricuspid annular motion velocities in normal hearts. J Cardiol. 2015;65:397-402.

13. Spruijt OA, Di Pasqua MC, Bogaard HJ, van der Bruggen CE, Oosterveer F, Marcus JT, et al. Serial assessment of right ventricular systolic function in patients with precapillary pulmonary hypertension using simple echocardiographic parameters: a comparison with cardiac magnetic resonance imaging. J Cardiol. 2017;69:182-8.

14. Bossone E, D'Andrea A, D'Alto M, Citro R, Argiento P, Ferrara F, et al. Echocardiography in pulmonary arterial hypertension: from diagnosis to prognosis. J Am Soc Echocardiogr. 2013;26:1-14.

11

15. American Thoracic Society/American College of Chest Physicians. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. Am J Respir Crit Care Med. 2003;167:211-77.

16. Garcia-Rio F, Romero D, Lores V, Casitas R, Herranz A, Galera R, et al. Dynamic Hyperinflation, Arterial Blood Oxygen, and Airway Oxidative Stress in Stable Patients With COPD. Chest. 2011;140(4):961-9.

17. Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. Am Rev Respir Dis. 1985;131:700-8.

18. O'Donnell DE, Webb KA. Exertional breathlessness in patients with chronic airflow limitation: the role of lung hyperinflation. Am Rev Respir Dis. 1993;148:1351-7.

19. Garcia-Rio F, Lores V, Mediano O, Rojo B, Hernanz A, López-Collazo E, et al. Daily physical activity in patients with chronic obstructive pulmonary disease is mainly associated with dynamic hyperinflation. Am J Respir Crit Care Med 2009;180:506-12.

20. Goda A, Lang CC, Williams P, Jones M, Farr MJ, Mancini DM. Usefulness of non-invasive measurement of cardiac output during sub-maximal exercise to predict outcome in patients with chronic heart failure. Am J Cardiol. 2009;104:1556-60.

21. Alonso-Fernández A, García-Río F, Arias MA, Mediano O, Pino JM, Martínez I, et al. Obstructive sleep apnoea-hypopnoea syndrome reversibly depresses cardiac response to exercise. Eur Heart J. 2006;27:207-15.

Table S1. Characteristics of the analysis procedures used for the determination of biomarkers in plasma and exhaled breath condensate

Sample/biomarker	Measurement procedure	Lower limit of detection	Intra-assay coefficient of variation
Plasma			
IL-17A	Immunology Multiplex Assay (Milliplex Human High Sensitivity T Cell HSTMAG-28SK-06, Merck Millipore Corp., Burlington, MA, USA)	0.20 pg/mL	0.18 %
IL-1β		0.18 pg/mL	0.62 %
IL-6		0.041 pg/mL	0.71 %
IL-8		0.12 pg/mL	0.097 %
MIP-1α		0.076 pg/mL	0.98 %
TNF-α		0.093 pg/mL	0.25 %
hsCRP	Turbidimetric method (Advia 2400, Siemens Healthcare Diagnostics, Erlangen, Germany)	0.03 mg/L	2.1%
8-isoprostane	Enzyme immunoassay (ab175819, Abcam, Cambridge, UK)	10 pg/mL	3.13 %
GPX1	Enzyme immunoassay (ab193767, Abcam)	0.4 ng/mL	2.6 %
Galectine-3	Enzyme immunoassay (ab188394, Abcam)	0,16 ng/mL	1.81 %
PIIINP	Enzyme immunoassay (SEA573hu, Cloud-Clone Corp., Katy, TX, USA)	62,5 pg/ml	2.34 %
hs-cTnT	Sandwich Chemiluminescent Immunoassay (Cobas e411 analyzer, Roche Diagnostics, Indianapolis, IN, USA)	3 ng/mL (pg/mL or ng/L)	2.6 %
NT-proBNP	One-step sandwich chemiluminescent immunoassay also based on LOCI technology	3 pg/mL	1.7
Homocysteine	Nephelometry based method (Dimension Vista, Siemens Healthcare Diagnostics)	2.0 µmoL/L	7%
Exhaled breath condensate			
IL-1β	Immunology Multiplex Assay (Milliplex Human High Sensitivity T Cell HSTMAG-28SK-04-6STD, Merck Millipore Corp.)	0.02 pg/mL	1.42 %
IL-6		0.01 pg/mL	1.89 %
IL-8		0.03 pg/mL	0.33 %
TNF-α		0.004 pg/mL	1.51 %

Definition of abbreviations: IL=interleukin; TNF-α=tumor necrosis factor α; MIP-1α=macrophage inflammatory protein-1α; hs-CRP=high sensitivity C-reactive protein; GSX=glutathione peroxidase; PIIINP=N-terminal type III procollagen; hs-cTnT=high sensitivity cardiac troponin T; NT-proBNP: N-terminal pro-B-type natriuretic peptide

Table S2. Comparison of lung parenchyma attenuation between COPD patients and control subjects*

	COPD group	Control group	*P*
Insp MLD, HU	-859 ± 24	-848 ± 19	0.061
Insp LAV, %	14.5 ± 10.7	4.4 ± 3.7	<0.001
Insp subrange 1, %	13.1 ± 9.0	4.1 ± 3.6	<0.001
Insp P15, HU	-942 ± 24	-923 ± 34	0.007
Exp MLD, HU	-804 ± 48	-710 ± 55	<0.001
Exp LAV, %	8.3 ± 9.2	0.6 ± 1.0	<0.001
Exp subrange 1, %	7.1 ± 7.5	0.5 ± 0.7	<0.001
Exp P15, HU	-916 ± 41	-849 ± 39	<0.001
Insp-exp MLD, HU	-55 ± 42	-138 ± 44	<0.001
Insp-exp LAV, %	6.2 ± 5.0	3.7 ± 3.9	0.033
Insp-exp subrange 1, %	5.9 ± 4.6	3.6 ± 3.7	0.029
Insp-exp P15, HU	-27 ± 29	-74 ± 54	0.001

Definition of abbreviations: Insp=inspiratory; Exp=expiratory; MLD=mean lung density; LAV=low attenuation volume; subrange 1 (-1000 to -951 HU); P15;15th percentile; HU=Hounsfield units.
*Values are mean ± SD and *P* values were obtained using Student's *t* tests.

Table S3. Comparison of biomarker levels between COPD patients and control

subjects*

	COPD patients	Control subjects	*P†*
IL17A, pg/mL	3.76 (2.72-5.63)	1.24 (0.31-2.72)	<0.001
IL-1β, pg/mL	0.98 (0.61-1.34)	0.35 (0.18-0.79)	<0.001
IL-6, pg/mL	1.59 (1.11-2.44)	1.01 (0.24-1.61)	0.003
IL-8, pg/mL	3.12 (1.92-3.79)	3.44 (2.64-4.81)	0.214
MIP-1α, pg/mL	10.21 (6.98-12.60)	7.19 (0.08-12.46)	0.049
TNFα, pg/mL	4.08 (3.09-5.72)	3.44 (2.67-3.78)	0.030
Homocysteine, µmoL/L	12.15 (10.65-15.05)	13.00 (10.50-14.15)	0.908
NT-proBNP, pg/mL	74.3 (35.8-204.3)	39.2 (26.5-111.6)	0.016
CRP, mg/L	3.02 (2.90-5.66)	2.90 (2.90-2.90)	0.001
hs-ctnT, ng/L	6.6 (3.7-13.4)	5.2 (4.1-7.4)	0.372
Galectine-3, ng/mL	4.0 (3.1-4.7)	2.8 (2.5-3.1)	<0.001
8-isoprostane, pg/mL	569 ± 150	507 ± 94	0.047
Glutathione peroxidases (GPX), mg/mL	3.9 (1.2-9.8)	0.4 (0.0-4.6)	0.003
N-terminal type III procollagen (PIIINP)	4550 (3877-5364)	4793 (3555-5725)	0.904
IL-1β in EBC, pg/mL	0.22 (0.20-0.32)	0.27 (0.19-0.37)	0.839
IL-6 in EBC, pg/mL	0.04 (0.03-0.07)	0.03 (0.03-0.10)	0.285
IL-8 in EBC, pg/mL	0.07 (0.05-0.15)	0.07 (0.06-0.20)	0.469
TNFα in EBC, pg/mL	0.27 (0.26-0.30)	0.26 (0.22-0.26)	0.001

Definition of abbreviations: IL=interleukin; MIP= macrophage inflammatory protein 1; TNF=tumor necrosis factor; NT-proBNP=N-terminal pro-B-type natriuretic peptide; CRP=C-reactive protein; hs-ctnT=high-sensitive cardiac troponin T; EBC=exhaled breath condensate

*Values are mean ± SD or median (interquartile range). †*P* values of comparisons performed by Mann-Whitney test or Student's *t* test.

Table S4. Comparison of echocardiographic parameters between COPD patients and

control subjects*

	COPD patients	Control subjects	*P*
LVEDD, cm	4.5 ± 0.5	4.7 ± 0.5	0.131
LVESD, cm	2.7 ± 0.5	0.8 ± 0.5	0.364
IVS, cm	1.0 ± 0.2	1.0 ± 0.2	0.786
LVPW, cm	1.0 ± 0.2	1.0 ± 0.2	0.788
LVEDV, mL	93 ± 23	100 ± 30	0.259
LVESV, mL	30 ± 11	32 ± 12	0.501
LV mass index, g/m^2	87.5 ± 18.4	93.4 ± 21.9	0.258
LVEF, %	68.5 ± 8.2	69.7 ± 7.0	0.548
LAA, cm^2	16.7 ± 4.0	19.4 ± 4.5	0.032
Maximal E-wave velocity, cm/s	74.5 ± 15.4	71.0 ± 12.5	0.323
Maximal A-wave velocity, cm/s	82.8 ± 21.4	68.4 ± 17.8	0.005
E/A ratio	0.94 ± 0.26	1.11 ± 0.37	0.034
Deceleration time, ms	232 ± 56	246 ± 56	0.374
e' wave, cm/s	10.6 ± 2.9	12.1 ± 3.0	0.040
E/e' ratio	7.5 ± 2.3	6.1 ± 1.3	0.010
RAA, cm^2	14.6 ± 3.5	16.9 ± 4.0	0.056
TAPSE, cm	2.2 ± 0.4	2.3 ± 0.3	0.107
PASP, mmHg	29.9 ± 11.7	21.6 ± 11.6	0.021

Definition of abbreviations: LVEDD: left ventricle end-diastolic diameter; LVESD: left ventricle end-systolic diameter; IVS: Interventricular septum; LVPW: posterior wall of left ventricle; LVEDV: left ventricle end-diastolic volume; LVESV: left ventricle end-systolic volume; LV: left ventricle; LVEF: Left ventricle ejection fraction; LAA: left atrial area; e': early diastolic mitral wave; RAA: right atrial area; TAPSE: tricuspid annular plane systolic excursion; PASP: pulmonary artery systolic pressure.

*Values are mean ± SD and *P*-values were obtained by Student's *t* test.

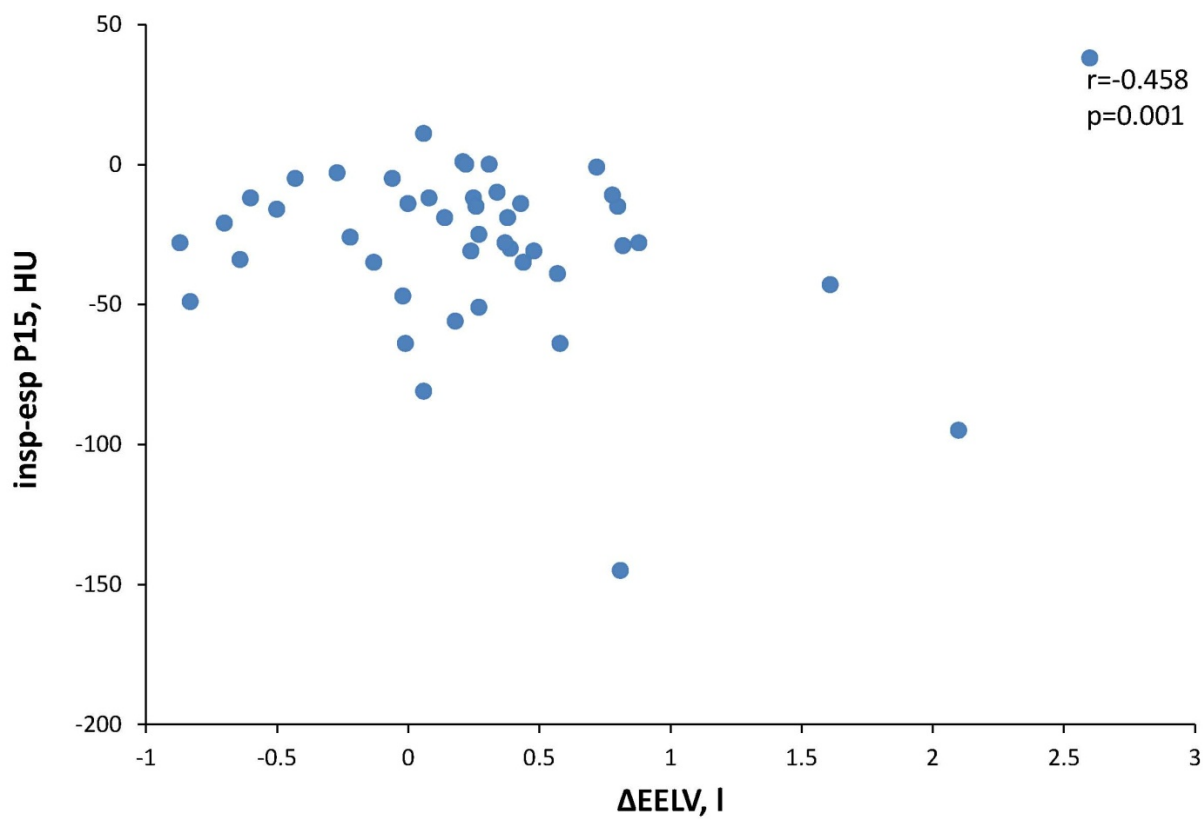**Table S5**. Comparison of lung densities in COPD patients with and without dynamic

hyperinflation*

	COPD patients with dynamic hyperinflation	COPD patients without dynamic hyperinflation	*P*
Insp MLD, HU	-863 ± 22	-849 ± 28	0.061
Insp LAV, %	15.9 ± 11.7	11.8 ± 7.6	0.221
Insp subrange 1, %	14.3 ± 9.7	10.8 ± 6.8	0.216
Insp P15, HU	-946 ± 23	-934 ± 25	0.100
Exp MLD, HU	-800 ± 52	-809 ± 36	0.534
Exp LAV, %	8.9 ± 10.7	7.1 ± 4.9	0.520
Exp subrange 1, %	7.6 ± 8.6	6.1 ± 4.2	0.549
Exp P15, HU	-914 ± 46	-919 ± 31	0.687
Insp-exp MLD, HU	-63 ± 45	-40 ± 30	0.070
Insp-exp LAV, %	7.0 ± 5.1	4.8 ± 4.4	0.151
Insp-exp subrange 1, %	6.7 ± 4.6	4.7 ± 4.2	0.153
Insp-exp P15, HU	-33 ± 30	-15 ± 23	0.052

Definition of abbreviations: Insp=inspiratory; Exp=expiratory; MLD=mean lung density; LAV=low attenuation volume; subrange 1 (-1000 to -951 HU); P15=15th percentile; HU=Hounsfield units
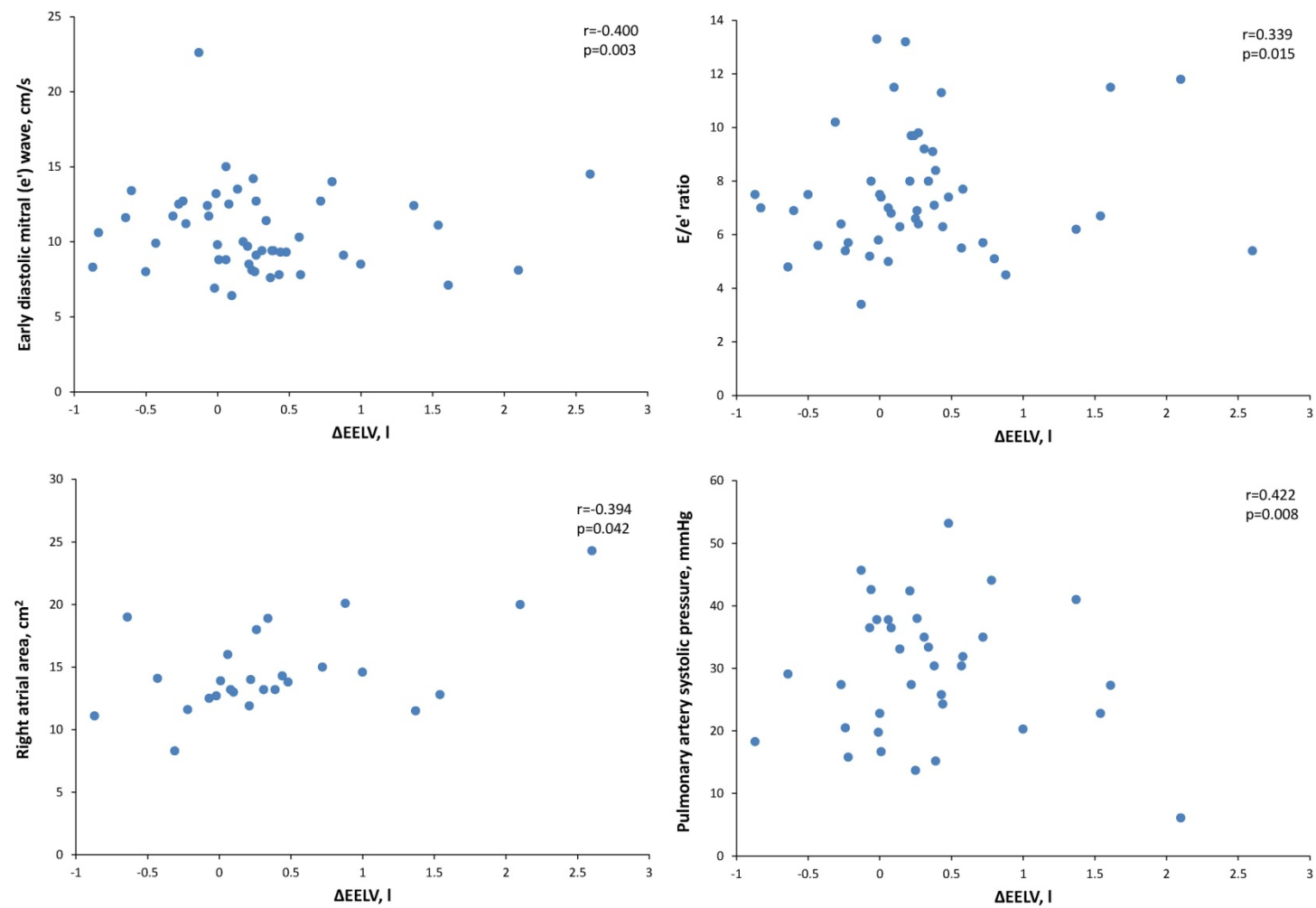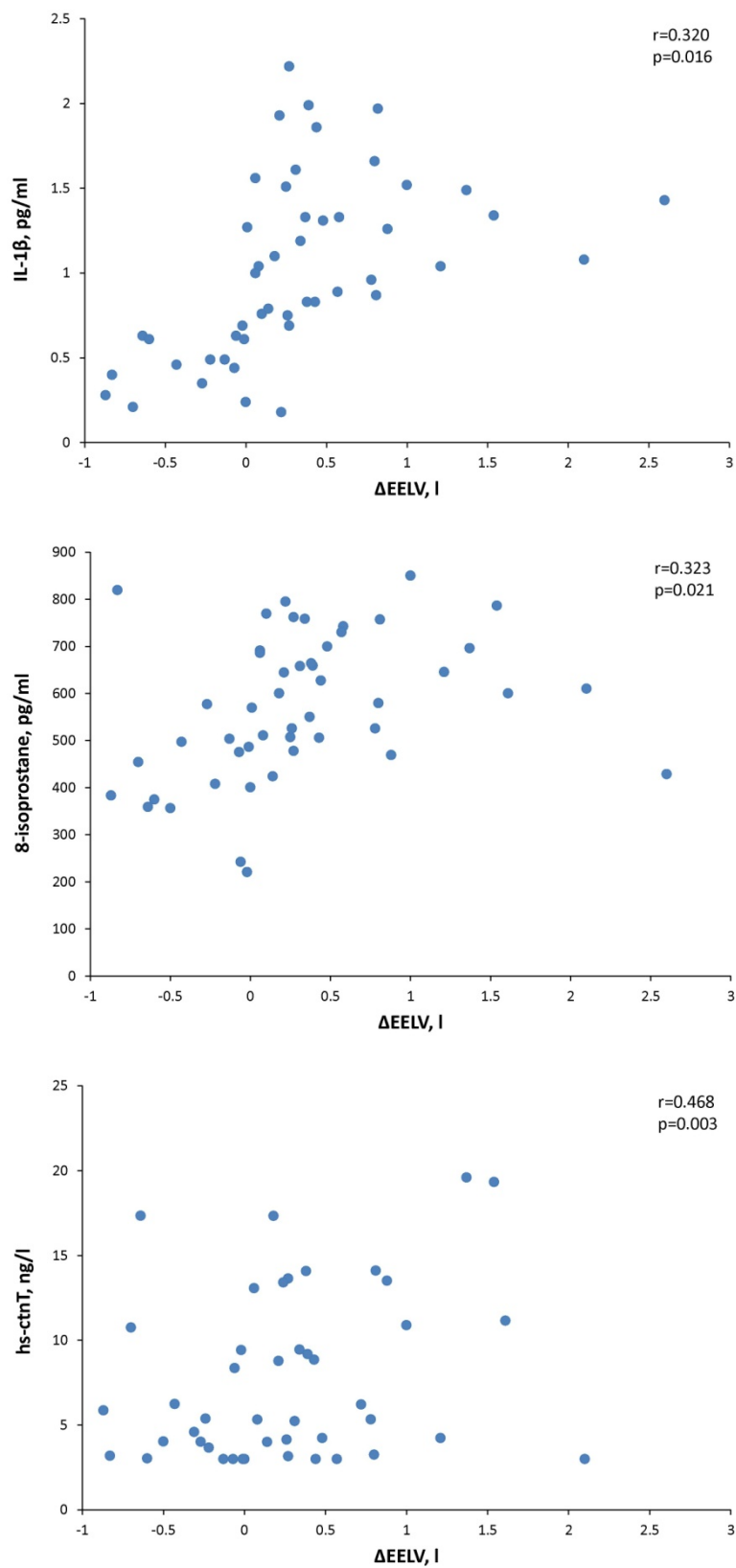*Values are mean ± SD and *P* values were obtained using the Student's *t* test.

FIGURES

Figure S1. Relationship between end-expiratory lung volume (EELV) increase and inspiratory-expiratory difference of the 15th percentile in COPD patients

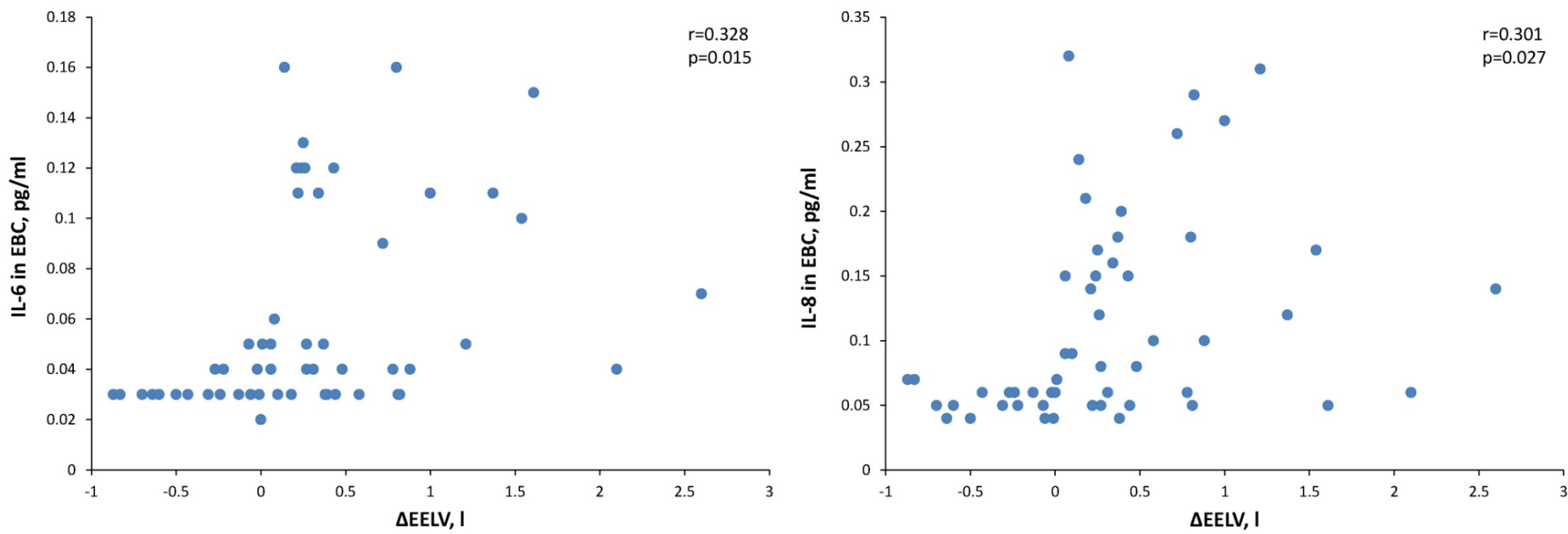**Figure S2**. Relationship between end-expiratory lung volume (EELV) increase and baseline echocardiographic parameters in COPD patients

Figure S3. Relationship between end-expiratory lung volume (EELV) increase and plasma levels of interleukin-1 ß, 8-isoprostane and high-sensitivity cardiac troponin T in COPD patients

20

Figure S4. Relationship between end-expiratory lung volume (EELV) increase and exhaled breath condensate (EBC) levels of interleukin (IL)-6 and 8 in COPD patients

Figure S5. Relationship between left ventricle end-diastolic diameter (LVEDD), plasma level of 8-isoprostane and exhaled breath condensate (EBC) levels of interleukin (IL)-6 and 8 with the stroke volume response to exercise ($\Delta SV/\Delta VO_2$) in COPD patients