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DEPARTMENT OF PHYSICAL EDUCATION AND SPORT SCIENCE

ASSOCIATION BETWEEN EMPHYSEMA DISTRIBUTION, DYNAMIC HYPERINFLATION AND MAXIMAL EXERCISE CAPACITY IN PATIENTS WITH COPD

της

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Μεταπτυχιακή Διατριβή που υποβάλλεται στο καθηγητικό σώμα για τη μερική εκπλήρωση των υποχρεώσεων απόκτησης του μεταπτυχιακού τίτλου του Προγράμματος Μεταπτυχιακών Σπουδών «Άσκηση και Υγεία» του Τμήματος Επιστήμης Φυσικής Αγωγής και Αθλητισμού του Πανεπιστημίου Θεσσαλίας.

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PREFACE AND AKNOWLEDGEMENTS

Chronic Obstructive Pulmonary Disease (COPD) is a chronic disorder with increasing prevalence, morbidity and mortality. It is characterized by non-reversible airflow limitation, which can be accompanied by several systemic manifestations. Progressive dyspnea, exercise limitation, muscle cachexia and frequent hospitalizations due to exacerbations, are only some of the consequences of COPD, particularly when the disease is advanced, that need to be addressed with specific treatments. Thus, further enlightenment of potential pathophysiologic mechanisms underlying COPD manifestations might provide valuable information in this direction. The current study was conducted under this scope, as part of a dissertation for the Master Program "Exercise and Health", for the University of Thessaly. The aim of the study was to investigate potential associations between emphysema distribution, which reflects the variability of pathologic presentation of the disease and dynamic hyperinflation, a physiologic parameter which reflects abnormalities in lung and chest mechanics and is particularly related to exertional dyspnea and limited functional capacity.

This dissertation comprises of three parts. The first part, the introduction, consists of two smaller sections. The first section is a relatively short but concise discussion on the definition, diagnosis, epidemiology and pathologic abnormalities of COPD, emphasizing on the variability of emphysema manifestation and distribution. The second section is an overview of lung hyperinflation. Its definition, measurement and natural history are described, while the pathophysiologic mechanisms of dynamic hyperinflation development

are given in more detail. This part ends with the primary and alternative study hypotheses, which were tested in the current dissertation.

The second part is a literature review regarding the association between emphysema distribution and several clinical and physiologic parameters in COPD. The four most relevant studies are being discussed with strengths and limitations commended. As it is concluded, data on the field are scarce and currently no study has evaluated the impact of emphysema distribution on dynamic hyperinflation and maximum exercise capacity among COPD patients, which constitutes the aim of the current dissertation.

Finally, the third part describes in detail the exact study protocol and its results. The recruitment of study population with inclusion and exclusion criteria, the primary and secondary variables measured and the measurement techniques used, the statistical analysis applied and the study results are presented in detail. The last section of this part is the discussion where the results, the strengths and limitations of the study are discussed and future potential applications of the findings are proposed.

I would really like to thank my supervisor Associate Professor Athanasio Jamurta from the department of Physical Education and Sports Science of University of Thessaly for our very good cooperation not only during the preparation of this thesis, but also during my attendance at the postgraduate course. Without his understanding and his unwavering confidence in my face regarding the data collection and the drafting of the thesis during my fellowship at the Respiratory Biomedical Research Unit of Royal Brompton Hospital in London, this dissertation could not have been completed.

I would also really like to thank Dr Michael Polkey, Professor of Respiratory Medicine at Royal Brompton Hospital in London and Dr Nicholas Hopkinson, Lecturer of Respiratory Medicine at Imperial College and Royal Brompton Hospital in London for giving me the

amazing chance to work with them at the Respiratory Biomedical Research Unit (BRU) at Royal Brompton Hospital. My fellowship there was a once-in a lifetime experience which significantly increased my skills both as a researcher and as a respiratory physician. I was really lucky to work with two experts in the area of COPD and to have the opportunity to participate in several projects carried out in the BRU, apart from the one used for my dissertation. I am really grateful for their contribution in defining the purpose of the current study and allowing me to use the BRU resources for its completion. I really hope that my fellowship there was just the beginning of a collaboration that will continue in the future.

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ABSTRACT (300 words)

Backrgound: Lung hyperinflation, a hallmark of Chronic Obstructive Pulmonary Disease (COPD), is the result of airflow limitation and emphysematous parenchymal destruction and is associated with dyspnea and exercise limitation. No study has yet evaluated the impact of emphysema distribution on dynamic hyperinflation (DH) and maximal exercise capacity among COPD patients.

Aim: To identify: a) the differences in the degree of DH during maximum cardiopulmonary exercise testing (CPET) between COPD patients with heterogeneous and matched COPD patients with homogeneous emphysema and b) the associations between emphysema distribution and CPET parameters in the two patient groups.

Material-Methods: Data on COPD patients who underwent thorax high-resolution computed tomography, full lung function measurements and CPET were retrospectively analysed. Resting inspiratory capacity (rIC) was calculated by averaging 4 resting IC maneuvers. ΔIC was calculated by subtracting the IC measured during the last 30 seconds of maximum exercise (peak IC), from rIC and was expressed as % percentage of rIC (ΔIC%). Emphysema quantification was conducted at 3 predefined levels for each patient using the syngo PULMO-CT (Siemens AG); a difference >25% between best and worse slice defined heterogeneous emphysema. Student's t-test was used for group comparison, after normality of distribution was assessed; level of $p<0.05$ was considered significant.

Results: Fifty patients who presented with heterogeneous (62.7% male; 60.9±7.5 years old; FEV_1%=32.4±11.4; TLCOc%=34.1±10) and 14 with homogeneous emphysema (61.5% male; 62.5±5.9 years old; FEV_1%=28.1±10.3; TLCOc%=33.3±11.5) fulfilled the

enrolment criteria. The two patient groups were matched for all baseline variables tested. ΔIC% was significantly higher among patients with homogeneous emphysema (39.8±9.8 vs.31.2±13, p=0.031), while no other CPET parameter was different between the groups. The presence of heterogeneity correlated positively with peak VO_2/HR %predicted, peak VO_2 %predicted and peak respiratory rate, and negatively with ΔIC%.

Conclusion: Homogeneous emphysema is associated with more DH during maximum exercise in COPD patients.

Keywords:

Chronic Obstructive Pulmonary Disease;

Dynamic Hyperinflation;

Emphysema Distribution;

Cardiopulmonary Exercise Testing

ΠΕΡΙΛΗΨΗ

Υπόβαθρο: Η πνευμονική υπερδιαταση, συνέπεια του περιορισμού της εκπνευστικής ροής και των εμφυσηματικών αλλοιώσεων του πνεύμονα στη Χρόνια Αποφρακτική Πνευμονοπάθεια (ΧΑΠ), σχετίζεται με δύσπνοια και μειωμένη ικανότητα άσκησης. Ωστόσο καμμία μελέτη δεν έχει διερευνήσει την επίδραση της κατανομης του εμφυσήματος στη δυναμική υπερδιάταση (ΔΥ) και τη μέγιστη ικανότητα για άσκηση των ασθενών με ΧΑΠ.

Σκοπός: Να διερευνηθούν: α) οι διαφορές στο βαθμό ΔΥ κατά την μέγιστη καρδιοαναπνευστική δοκιμασία άσκησης (ΚΑΔΑ) μεταξύ ασθενών με ετερογενές και όμοιων ασθενών με ομοιογενές εμφύσημα και β) οι συσχετίσεις ανάμεσα στην κατανομή του εμφυσήματος και της παραμέτρους της ΚΑΔΑ στις δύο ομάδες.

Υλικό-Μέθοδοι: Στην αναδρομική μελέτη εντάχθηκαν ασθενείς με ΧΑΠ που υποβλήθηκαν σε αξονική τομογραφία θώρακος υψηλής ευκρίνειας, πλήρη έλεγχο αναπνευστικής λειτουργίας και μέγιστη ΚΑΔΑ. Η εισπνευστική χωρητικότητα ηρεμίας (rIC) υπολογίστηκε από τον μέσο όρο 4 προσπαθειών ηρεμίας. Το ΔIC υπολογίστηκε αφαιρώντας την μέγιστη IC, δηλαδή την μετρούμενη στα τελευταία 30 δευτερόλεπτα της μέγιστης άσκησης από την rIC και εκφράστηκε ως % αναλογία της rIC (ΔIC%). Η ποσοτικοποίηση του εμφυσήματος έγινε σε 3 προκαθορισμένα επίπεδα για κάθε ασθενή με το syngo PULMO-CT (Siemens AG). Η διαφορά>25% μεταξύ καλύτερης και χειρότερης τομής όρισε το ετερογενές εμφύσημα. Χρησιμοποιήθηκε το Student’s t-test για συγκρίσεις μεταξύ των ομάδων, έπειτα από εκτίμηση της κανονικότητας της κατανομής των μεταβλητών. Επίπεδο $p<0.05$ ορίστηκε ως σημαντικό.

Αποτελέσματα: Πενήντα ασθενείς με ετερογενές (60.9±7.5 ετών με FEV_1%=32.4±11.4 και TLCOc%=34.1±10) και 14 με ομοιογενές εμφύσημα (62.5±5.9 ετών με FEV_1%=28.1±10.3 και TLCOc%=33.3±11.5) πληρούσαν τα κριτήρια εισαγωγής. Οι δύο ομάδες ασθενών ήταν όμοιες για το σύνολο των παραμέτρων ηρεμίας. Η ΔIC% ήταν σημαντικά υψηλότερη στους ασθενείς με ομοιογενές εμφύσημα (39.8±9.8 vs.31.2±13, p=0.031), ενώ καμμία άλλη παράμετρος της ΚΑΔΑ δε διέφερε μεταξύ των ομάδων. Η παρουσία ετερογένειας συσχετίζονταν θετικά με τις peak VO_2/HR %predicted, peak VO_2 %predicted και τη μέγιστη αναπνευστική συχνότητα και αρνητικά με την ΔIC%.

Συμπέρασμα: Το ομοιογενές εμφύσημα συνοδεύεται από μεγαλύτερη ΔΥ κατά τη διάρκεια μέγιστης άσκησης σε ασθενείς με ΧΑΠ.

Λέξεις-κλειδιά:

Χρόνια Αποφρακτική Πνευμονοπάθεια

Δυναμική Υπερδιάταση

Κατανομή του εμφυσήματος

Καρδιοαναπνευστική Δοκιμασία Άσκησης

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LIST OF ABBREVIATIONS

6MWT: 6 Minute Walking Test

AT: Anaerobic Threshold

ATS: American Thoracic Society

BMI: Body Mass Index

BODE: B for Body Mass Index, O for Obstruction, D for Dyspnea and E for Exercise capacity

CPET: Cardiopulmonary Exercise Testing

COPD: Chronic obstructive Pulmonary Disease

CT: Computed Tomography

DH: Dynamic hyperinflation

EELV: End Expiratory Lung Volume

EILV: End inspiratory lung volume

ERS: European Respiratory Society

FEV_1: Forced Expiratory Volume in 1 second

FRC: Functional Residual Capacity

FVC: Forced Vital Capacity

GOLD: Global Initiative for Obstructive Lung Disease

Het group: Group with Heterogeneous emphysema

Hom group: Group with Homogeneous emphysema

HR: Heart Rate

HRCT: High Resolution Computed Tomography

HU: Hounsfield Units

IC: Inspiratory Capacity

KCOc: Carbon Monoxide Diffusion Coefficient adjusted for hemoglobin concentration

LLN: Lower Limit of Normal

LVR: Lung Volume Reduction

NANHES III: Third National Nutrition and Examination Survey

$PaCO_2$: arterial Carbon Dioxide Partial Pressure

PaO_2: arterial Oxygen Partial Pressure

PASW (Predictive Analytics Software by SPSS

PEEP: Positive End Expiratory Pressure

$PETCO_2$@AT: End-Tidal carbon dioxide at AT

$PETCO_2$@VO_2 peak: End-Tidal carbon dioxide at peak VO_2

$PETO_2$@VO2 peak: End-Tidal oxygen at peak VO_2

$PETO_2$@AT: End-Tidal oxygen at AT

PFTs: Pulmonary Function Testing parameters

pIC: Peak IC

PLATINO: Latin American Project for the Investigation of Obstructive Lung Disease

RER: Respiratory Exchange Ratio

rIC: Rest IC

RR: Respiratory Rate

RV: Residual Volume

SaO_2: pulse Oximetry (arterial oxygen Saturation)

Te = Expiratory Time

TLC: Total Lung Capacity

TLCOc: Carbon Monoxide Diffusion Capacity adjusted for hemoglobin concentration

Trs =time constant for emptying of the respiratory system

UM/L: average emphysema score of the upper and middle slice versus average emphysema score of the lower slice

V_E: minute Ventilation

V_E/VCO_2@AT: Ventilatory Equivalent for Carbon Dioxide at AT

V_E/VCO_2@VO_2 peak: Ventilatory Equivalent for Carbon Dioxide at peak VO_2

Vr = Relaxation Volume

Vt: Tidal Volume

VO_2: Oxygen Uptake

VCO_2: Carbon Dioxide production

VO_2/HR@AT: Oxygen Pulse at AT

VO_2/HR@VO_2 peak: Oxygen Pulse at peak VO_2

VO_2/HR@AT: Oxygen Pulse at AT

WR: Work Rate

ΔIC: change of IC from rest to peak

I.INTRODUCTION

A. Chronic Obstructive Pulmonary Disease

Definition, diagnosis and classification of severity

According to a working definition of Global Initiative for Chronic Obstructive Lung Disease (GOLD), Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.(Global Initiative for Chronic Obstructive Lung Disease, 2014)

The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. The presence and severity of airflow limitation is best evaluated with spirometry, which is the most widely used test for lung function assessment.(Global Initiative for Chronic Obstructive Lung Disease, 2014)

COPD may be present in any individual who has been exposed to risk factors for COPD, and is manifesting or not relevant symptoms (cough, sputum and/or dyspnea).(Celli, MacNee, & ATS/ERS Task Force, 2004) However, a definite COPD diagnosis is made by spirometric rather than clinical criteria. According to GOLD and American Thoracic Society (ATS) / European Respiratory Society (ERS) guidelines, a ratio of Forced Expiratory Volume in 1 second (FEV_1) to Forced Vital Capacity (FVC) < 0.7 post bronchodilation is the essential criterion to confirm the presence of not fully reversible

airflow obstruction.(Celli et al., 2004)(Global Initiative for Chronic Obstructive Lung Disease, 2014)

A large population study indicated that the use of the post bronchodilation FEV_1/FVC ratio was higher than 0.7 in all age groups, supporting its use as a diagnostic criterion.(Johannessen et al., 2006) However, it has been suggested that the use of a fixed ratio may result to overdiagnosis of COPD in the elderly, due to the aging process of the lung and to the underdiagnosis of COPD in adults younger than 45 years old.(Celli, Halbert, Isonaka, & Schau, 2003; Cerveri et al., 2008) Using the lower limit of normal (LLN) values for the FEV_1/FVC ratio, based on the normal distribution of values, and classifying the bottom 5% as abnormal, is one way to correct potential misclassifications. Practically, all programmable spirometers could do this calculation if reference equations for the LLN values of FEV_1/FVC ratio were available.(Cerveri et al., 2008; Global Initiative for Chronic Obstructive Lung Disease, 2014)

The typical symptoms of COPD are cough, sputum and dyspnea; nevertheless the association between the severity of airflow limitation and the presence of symptoms is imperfect. Cough and sputum could precede airflow limitation for many years, and airflow limitation could be present with minimal symptoms.(Global Initiative for Chronic Obstructive Lung Disease, 2014) Thus, the categorization of disease severity based on spirometric criteria is a pragmatic approach, useful for practical implementation. According to ATS/ERS and GOLD guidelines, COPD severity is classified in four stages:(Celli et al., 2004)(Global Initiative for Chronic Obstructive Lung Disease, 2014)

a) Stage I or mild COPD (FEV_1/FVC <0.7; FEV1≥80% predicted) where symptoms of airflow obstruction are often not present

b) Stage II or Moderate COPD (FEV_1/FVC <0.7; 50%≥FEV_1%predicted<80%). In this stage cough and sputum might be present and dyspnea typically develops during exercise

c) Stage III or Severe COPD (FEV_1/FVC <0.7; 30%≥FEV_1%predicted<50%). In this stage dyspnea is typically more severe, sputum and cough are present most of the time and patients present with limited exercise capacity, fatigue and repeated exacerbations

d) Stage IV or Very Severe COPD (FEV_1/FVC <0.7; FEV_1%predicted<30% or 30%≥FEV_1%predicted<50% plus chronic respiratory failure). Respiratory failure is defined as an arterial partial pressure of oxygen (PaO_2) less than 8.0 kPa (60 mm Hg), with or without arterial partial pressure of carbon dioxide ($PaCO_2$) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level. At this stage quality of life is severely impaired and exacerbations could be life-threatening

COPD aetiology and burden

Cigarette smoking is the most commonly encountered risk factor for the development of COPD worldwide. In USA 80-90% of COPD cases are attributed to smoking(Senior & Atkinson, 2008) and previous studies have indicated that there is a causal association between cigarette smoking and COPD development.(Office of the Surgeon General (US) & Office on Smoking and Health (US), 2004) However, the use of biomass fuel for heating and cooking in poorly ventilated rooms is becoming a major risk factor for COPD development, mainly among non-smoking women in developing countries.(Salvi & Barnes, 2009) Apart from tobacco and biomass exposure, several other risk factors, related either to the "host" or the environment have been identified and are presented in Table 1. COPD development is the final result of the cumulative exposure to one or more risk factors over a period of decades.(Siafakas et al., 1995; Global Initiative for Chronic Obstructive Lung Disease, 2014)

Table 1. Risk factors for the development of COPD

Risk factors related to the host
Age
Gender
Genes (e.g. alpha1 deficiency)
Risk factors related to the environment
Exposure to particles and fumes
-tobacco smoking
-indoor air pollution from heating and cooking with biomass
-occupational organic and inorganic dust
-outdoor air pollution
Lung growth and development
Oxidative stress
Respiratory Infections
History of tuberculosis
Socioeconomic status
Nutrition

COPD is a major health problem worldwide with substantial social and economic burden. Of all the major chronic diseases, COPD is the one whose burden is rising fastest, and it is now the third leading cause of death worldwide.(Lozano et al., 2012) Both its prevalence and burden are going to increase in the future,(Mathers & Loncar, 2006) due to the growing exposure to major risk factors and particularly cigarette smoking and because of the increasing age of the world population. The increase of age can impact the prevalence

of COPD in two ways: the population is exposed to COPD risk factors for more years and lives longer to manifest the symptoms and signs of the disease. Moreover, aging itself induces several lung parenchymal changes that resemble COPD.(Maciewicz, Warburton, & Rennard, 2009)

The exact prevalence of COPD varies between studies and countries, not only due to the unique characteristics of the population investigated, but also because of the discrepancy in diagnostic criteria and research tools used, (van den Boom et al., 1998; Halbert, Isonaka, George, & Iqbal, 2003) so results are not easily comparable. The Third National Nutrition and Examination Survey (NANHES III) indicated that 13.9% of adult population in USA suffers from COPD.(Mannino & Braman, 2007) The multicentre Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) which was conducted in Central and Latin America reported a COPD prevalence which varied between sites from 7.8% to 19.4%.(Menezes et al., 2005) In Europe, a population study conducted in Northern Italy reported a COPD prevalence of 18.3%,(Viegi et al., 2000) although the frequency of COPD varies hugely between countries. Beyond these variations, it has been estimated that COPD is the major cause of death from respiratory diseases in Europe.(Viegi et al., 2007)

COPD pathology and pathophysiology

Cigarette smoking, biomass fuel and/or other of toxic particles inhalation lead to airway inflammation. This normal defensive mechanism of the host is abnormally amplified in patients with COPD, may result in abnormal mucus hypersecretion (chronic bronchitis), tissue destruction (emphysema), and destruction of normal repair and defense mechanisms, causing small airway inflammation and fibrosis (bronchiolitis). These pathologic changes result in increased resistance to airflow, particularly in the small conducting airways and increased compliance of the lungs, resulting to air trapping and progressive airflow

obstruction.(MacNee, 2008) Similar to other chronic inflammatory conditions, the role of cytokines in the development of this pathology is major, although not fully clarified.(Global Initiative for Chronic Obstructive Lung Disease, 2014)(Barnes, 2009) The complex pathologic features of COPD could be grouped in three entities: chronic bronchitis, small airways disease and emphysema. In an individual COPD patient these three pathologic components coexist to varying degrees and contribute distinctively to the abnormalities in lung function, chest wall mechanics and gas exchange.(Russi, Bloch, & Weder, 1999)

Chronic bronchitis is a disease of the larger airways (>2-4 mm) characterized by bronchial gland enlargements and chronic mucus hypersecretion.(Russi et al., 1999; MacNee, 2008) Mucus is produced by mucus glands in the larger airways and by goblet cells in the airway epithelium. In healthy subjects the number of goblet cells is decreased from central to peripheral airways, while these cells are totally absent in terminal bronchioles. By contrast, in smokers and COPD patients the mean number of golblet cells is increased and they are found more peripherally. Moreover, the mucocilliary escalator is impaired and squamous metaplasia of the airway epithelium along with increased smooth muscle and connective tissue is found in bronchial biopsies.(MacNee, 2008) Small airways disease or bronchiolitis is a disease of the airways <2 mm diameter (small bronchi and bronchioles), which is the major site of airflow obstruction in COPD. Small airways disease is one of the first pathologic abnormalities to occur. Increased inflammation is the predominant manifestation; the inflammatory cell changes in the small airways are similar to those in larger airways with increased $CD8^+$ lymphocytes and CD8/CD4 ratio, leading to their narrowing and eventually obstruction.(Russi et al., 1999; MacNee, 2008)

Contrary to chronic bronchitis and small airways disease, which generally involve distinct and well defined parts of the airways, the distribution of pulmonary emphysema

development in the lung is more variable. Pulmonary emphysema is defined as abnormal and permanent enlargement of airspaces distal to the terminal bronchioles accompanied by destruction of their wall and without obvious fibrosis.(Viegi et al., 2007) The major types of emphysema are distinguished based on the distribution of enlarged airspaces within the acinar unit, which is the lung parenchyma unit supplied by a single terminal bronchiole. Three major types of emphysema have been described: a) centriacinar or centrilobular emphysema, where the airspaces are distributed around the terminal bronchiole. This type of emphysema begins in the respiratory bronchioles and spreads peripherally, b) panacinar or panlobular emphysema, where the airspaces are distributed throughout the acinar unit uniformly and c) periacinar or paraseptal or distal acinar emphysema. It predominantly involves alveolar ducts and sacs, the distal portion of the acinus and the enlarged airspaces are found along the edge of the acinar unit, against a fixed structure. (Russi et al., 1999; MacNee, 2008) Bullous disease of the lung is an additional distinct form of emphysema, characterized by large and eventually growing bullae, which may compress adjacent relatively "healthy" lung. To further increase the variation of emphysema manifestation, combinations of these various forms of emphysema coexist in many patients.(Russi et al., 1999)

Contrary to chronic bronchitis and small airways disease, which generally involve distinct and well defined parts of the airways, emphysema distribution in the lung is more variable and emphysema patterns may significantly differ between individuals. Emphysema is characterized as heterogeneous when distinct areas of destroyed parenchyma as well as relatively well-preserved lung tissue coexist.(Russi et al., 1999) When the areas of destroyed parenchyma are distributed throughout the lung and there are no lobes with obvious predominance of involvement, emphysema is characterized as homogeneous. To describe this variability, a simplified surgically oriented classification system based on CT

findings has been previously proposed, which considers the predominance of the involved lobes and distinguishes between: 1) homogeneous (with patchy areas or completely homogeneous), 2) moderately heterogeneous and 3) markedly heterogeneous (upper lobe, upper lobe and apical segment (lower lobe) or lower lobe) emphysema distribution.(Weder et al., 1997) Although this is not the only classification system proposed in literature, the general categorization of emphysema distribution in homogeneous and heterogeneous have been proven clinically useful, particularly for the selection of patients eligible for invasive treatments, such as lung volume reduction procedures.(S. J. Clark et al., 2014)

B. Lung Hyperinflation: An Overview

Definition, measurement and natural history of Lung Hyperinflation

Lung hyperinflation is defined as an abnormal increase in the volume of air remaining in the lungs or in a region of a lung at the end of spontaneous expiration, that is in the end-expiratory lung volume (EELV). The presence of lung hyperinflation is very frequent in COPD and is due to the combined effects of increased lung compliance, as a result of the permanently destructive changes of emphysema, and the development of expiratory flow limitation.(O'Donnell, 2006)

Lung hyperinflation could be static, dynamic or both. Pulmonary static or resting hyperinflation refers to the permanent increase of EELV among COPD patients, compared to healthy subjects. It is mainly due to the destruction of pulmonary parenchyma and loss of elastic lung recoil and it is present during rest.(Tzani et al., 2011) Since inert gas dilution techniques may underestimate absolute lung volumes due to the presence of non-communicating airways, body plethysmography remains the gold standard for the measurement of EELV and has been shown to be reliable. Another conventional measure of resting lung hyperinflation that has been used is the increase of total lung capacity

(TLC) more than 120% of predicted and/or the increase of other volume compartments (e.g. Residual volume (RV)) above the upper limits of normal. In practice, values exceeding these thresholds seem to be clinically important, however no consensus definition or a formal staging system for the severity of static hyperinflation currently exist.(O'Donnell & Laveneziana, 2006)

In addition to or independently from static hyperinflation, dynamic hyperinflation (DH) of the lung may be observed at any stage of COPD. (O'Donnell, 2008; Tzani et al., 2011) DH refers to the variable and temporary increase in EELV above its baseline value, which occurs when in situations where expiratory flow limitation is suddenly worsened (i.e. during exacerbations) or when ventilatory demand is acutely increased, as it happens during exertion, anxiety, or transient hypoxaemia.(O'Donnell & Parker, 2006; Guenette, Chin, Cory, Webb, & O'Donnell, 2013; Thomas, Decramer, & O'Donnell, 2013) DH is usually measured by serial Inspiratory Capacity (IC) maneuvers which accurately reflect changes in EELV provided that TLC remains unaltered. The technique is described in detail later, in the methods section. EELV changes are distinct from changes in end-inspiratory lung volume (EILV); the latter represents the combination of change in EELV and expansion of Tidal Volume (Vt) during exercise, and is not a measure of DH.(Guenette et al., 2013)

Expiratory flow limitation and dynamic hyperinflation are clinical and pathologic concepts that have been identified more than 100 years ago; However, recent developments have revitalized the interest on these pathophysiological consequences of obstructive disease, with a provocative hypothesis recently proposing that the transition from peripheral airways disease to COPD follows the progress of severity of expiratory flow limitation.(Milic-Emili, 2004; Puente-Maestu & Stringer, 2006) The natural history of the development of lung hyperinflation in COPD patients remains unknown, because no

formal epidemiological studies exist; nevertheless, clinical experience indicates that hyperinflation develops slowly and insidiously over many years, similar to the decline in FEV_1. It seems that closing volume and RV are the first volume components to increase, due to increased airway closure. EELV increases thereafter, reflecting the effects of worsening expiratory flow-limitation and alteration in static lung mechanics. Eventually, TLC increases along with lung compliance.(O'Donnell, 2006; O'Donnell & Laveneziana, 2006) Although the negative effects of lung hyperinflation are not usually perceived by the patients until the disease is quite advanced, preliminary data indicate that EELV may be significantly increased even in patients with early stages of COPD.(O'Donnell & Laveneziana, 2006) This is why longitudinal studies in large COPD populations are required, in order to define the exact time course of volume changes in the various lung compartments during disease progression.

Pathophysiology of dynamic hyperinflation

In health, the relaxation volume of the respiratory system is dictated by the balance of forces between the inward elastic recoil pressure of the lung and the outward recoil pressure of chest wall. The equilibrium point is the lung volume where the net elastic recoil of the total respiratory system is zero. In healthy individuals the EELV during relaxed tidal breathing is approximately equal to the equilibrium point of the respiratory system.(O'Donnell & Laveneziana, 2006)

In COPD, the elastic recoil of the lung is decreased due to the parenchymal desctruction, resulting to a higher relaxation volume compared to age-matched individuals; This condition is termed "static hyperinflation". The EELV is also different compared to healthy individuals. Due to the expiratory flow limitation, the time needed for lung units to empty their volume and achieve their passive equilibrium point is significantly higher and

many of them do not reach their relaxation volume before a new inspiration is initiated. As a result, part of the gas that would have been expired, if alveolar units were not destroyed due to emphysema, remains "trapped" within the lung. This is why EELV is increased compared to the expected relaxation volume, even during resting tidal breathing and the alveolar pressure at the end of the expiration is higher than the atmospheric pressure (intrinsic Positive End Expiratory Pressure (PEEP)).(Pride & Macklem, 1986; Younes, 1991; O'Donnell & Laveneziana, 2006; Puente-Maestu & Stringer, 2006) The exact value of EELV in patients with COPD varies with the severity of expiratory flow-limitation, the effect of time-dependent parameters and the breathing pattern and is described by the following equation:

$$EELV - Vr = V_t/e^{Te/Trs} - 1$$

where Vr = relaxation volume, Te = expiratory time, Trs =time constant for emptying of the respiratory system, V_t = tidal volume, and base e = 2.718282. (Vinegar, Sinnett, & Leith, 1979) This equation indicates that any increase in tidal volume, decrease in expiratory time or both could result to an elevation of EELV.

During exercise minute ventilation must be increased in order to meet the elevated metabolic demands. This is achieved by increasing both the tidal volume and the respiratory rate (RR), which means that the expiratory time necessary to reach relaxation volume is reduced. In normal young subjects expiratory flow is fast enough to decrease end-expiratory lung volume.(Pride & Macklem, 1986; Henke, Sharratt, Pegelow, & Dempsey, 1988) In older subjects, EELV also decreases during moderate exercise, but tends to increase back to its resting levels in exercise of higher intensity.(Johnson, Reddan, Seow, & Dempsey, 1991) In COPD, as exercise is progressing more and more alveolar units are unable to empty their gas, because expiratory time decreases when the respiratory

rate increases, resulting in a typical rise in EELV. This acute increase in EELV above its baseline value is called DH and its degree is inversely related to the level of resting lung hyperinflation.(O'Donnell, Revill, & Webb, 2001; Puente-Maestu et al., 2005; Puente-Maestu & Stringer, 2006)

Pathophysiological and clinical consequences of DH

The acute increase of lung hyperinflation, such as during exercise, is accompanied by several negative consequences, due to the altered respiratory mechanics.(O'Donnell & Laveneziana, 2006) DH results in sudden increases in the elastic loads on the inspiratory muscles as tidal volume is forced to operate at the upper extreme of the respiratory system's pressure-volume relation, thus increasing the work and oxygen cost of breathing.(O'Donnell, Bertley, Chau, & Webb, 1997) Due to the maximal shortening of the diaphragm muscle fibers and the increased mechanical loading, DH can predispose inspiratory muscles to fatigue.(Sinderby et al., 2001) Moreover, DH poses a mechanical "barrier" for tidal volume to appropriately increase during exercise, resulting in ventilatory exercise limitation. In patients with severe ventilation-perfusion abnormalities this inability to further increase tidal volume can result to arterial desaturation and retention of carbon dioxide during exercise.(O'Donnell, D'Arsigny, Fitzpatrick, & Webb, 2002)

Furthermore, DH negatively affects cardiac function in various ways.(Puente-Maestu & Stringer, 2006) Right ventricular preload is usually reduced due to decreased venous return.(Miller, Pegelow, Jacques, & Dempsey, 2005) Alternatively, right ventricular afterload could be increased due to high pulmonary vascular resistance associated with breathing in lung volumes close to TLC.(Oswald-Mammosser et al., 1998; Ranieri, Dambrosio, & Brienza, 1996) Finally, left ventricular afterload might be increased, since

large swings of intrathoracic pressure during exercise may result to left cardiac dysfunction.(Montes de Oca, Rassulo, & Celli, 1996)

Several clinical manifestations of DH have been previously reported in literature, with exercise limitation being one of the most characteristic. COPD patients establish a poor exercise performance, either during submaximal exercise, where they present with reduced endurance or during maximum exercise, where they establish marked reductions in peak oxygen consumption.(Gallagher, 1994; Puente-Maestu & Stringer, 2006; Tzani et al., 2011). Moreover, DH has been previously associated with increased dyspnea, mainly during exercise and exacerbations. In these conditions the respiratory drive is acutely increased but the ability of ventilation to match the increased needs is greatly hampered, so dyspnea becomes intolerable very quickly for most COPD patients;(Thomas et al., 2013) these exercise abnormalities could be further accompanied by exertional desaturation and/or hypercapnia, as already been discussed. Furthermore, DH might have a prognostic impact in COPD. Literature data indicate a potential correlation between lung hyperinflation, COPD exacerbations (Zaman, Mahmood, & Altayeh, 2010) and annual decline of FEV_1 among COPD patients,(Yuan et al., 2009) while resting hyperinflation has been previously reported as an independent predictor of respiratory and all-cause mortality in COPD.(Casanova et al., 2005)

C. Study hypothesis

As already discussed, DH is the result of increased lung compliance and expiratory flow limitation, which are both developed because of the disarrangement of the lung structure. The outer attachments of small bronchi and bronchioles to the adjacent alveolar walls maintain the tubular integrity of the airways. Loss of these attachments due to emphysema results to distortion and irregularities of the airways because of the loss of lung elastic

recoil, which may also lead to airflow limitation.(MacNee, 2008) So the question which arises is whether the distribution of these abnormalities (irregular, such as in heterogeneous emphysema or more uniform, such as in homogeneous emphysema) is associated with the severity of DH and the establishment of its consequences among COPD patients.

Primary study hypothesis

Null Primary Hypothesis (H_0): There is no difference in dynamic hyperinflation between COPD patients with homogeneous compared to matched COPD patients with heterogeneous emphysema

Alternative Primary Hypothesis (H_1): Dynamic hyperinflation differs significantly between COPD patients with homogeneous and matched COPD patients with heterogeneous emphysema.

Secondary Study Hypothesis

Null Secondary Hypothesis: There is no difference in maximal exercise parameters between COPD patients with homogeneous and matched COPD patients with heterogeneous emphysema

Alternative Secondary Hypothesis: There are statistically significant differences in one or more maximal exercise parameters between COPD patients with homogeneous and matched COPD patients with heterogeneous emphysema

II. LITERATURE REVIEW

Currently, most of the published literature regarding the impact of emphysema distribution on clinical outcomes in COPD is related to lung volume reduction (LVR) procedures, either surgical or bronchoscopic. When the criterion of heterogeneity and particularly upper lobe disease is fulfilled, patients present with improved exercise capacity,(Wan et al., 2006) functional improvement in terms of FEV_1,(Wisser et al., 1998) better health related quality of life,(Wood et al., 2007) and improved survival (Fishman et al., 2003), after the procedure. However, rest of data regarding the association between a patient's clinical phenotype and emphysema distribution are scarce and, to the author's knowledge, no study has yet evaluated its impact on DH during maximal exercise.

One of the first studies on the field that assessed the effect of emphysema distribution on functional and clinical characteristics was conducted by Parr, Stoel, Stock & Stockley (2004). The authors studied 102 patients, 65 of whom had predominantly basal and the rest had predominately apical emphysema. The two groups were matched for emphysema volume and age and authors utilized matched pair analysis in order to identify potential differences in functional parameters, according to emphysema distribution. Basal emphysema distribution was associated with a greater impairment of FEV_1, but less impairment of gas transfer (as measured by diffusion coefficient for carbon monoxide (KCO)), compared to apical distribution.(Parr et al., 2004).

This study indicated that emphysema distribution may have an impact on lung physiologic parameters; however, it carried several limitations. The most important is that it was conducted in patients with severe alpha1 deficiency. Although these patients present with emphysema, its pathogenetic mechanism and pathology is quite different from the one of COPD. Moreover, in alpha1 deficiency emphysema usually predominates in lower lobes,

while in COPD it usually predominates in upper lobes,(Russi et al., 1999) when it is heterogeneous. Finally, authors did not investigate at all the potential impact of emphysema distribution on DH and other exercise variables.

Another study of alpha1 deficiency patients, which was conducted later confirmed this association between emphysema distribution and pulmonary function parameters. Fifteen patients with normal FEV_1 and KCO were compared to three groups of patients with various combinations of FEV_1 and/or KCO abnormalities. Again, the authors concluded that lower zone emphysema is associated with worse FEV_1 values and better KCO values, compared to upper zone emphysema.(Holme & Stockley, 2007) Likewise, this was a study conducted in a non-COPD population, while any potential associations with DH or other exercise parameters were not studied.

One of the most important studies in the field, in terms of various types of emphysema distribution tested, was the one of Mair et al (2009). One hundred twenty nine COPD patients with smoking-related disease underwent CT assessment of the extent and distribution of their emphysema and were categorized as upper/lower zone and core/rind predominant. Core predominance was associated with more impaired resting pulmonary function, worse dyspnea and higher BODE (B: Body Mass Index, O:Obstruction, D: Dyspnea and E: exercise capacity) index, while upper predominance was associated with higher scores in St George Respiratory Questionnaire. The authors concluded that the core/rind categorization of emphysema distribution correlates well with clinical features among COPD patients.(Mair et al., 2009) Although this is a study conducted in a relatively big cohort of COPD patients it carries two limitations: core predominance could be present either in patients with homogeneous or in patients with heterogeneous emphysema, so which of these two emphysema distribution entities correlates best with clinical parameters

cannot be distinguished. The second limitation is that, like in previous studies in the field, the impact of emphysema distribution on DH was not investigated.

Contrary to the previous studies, de Torres et al (2011) failed to establish any associations between clinical parameters and emphysema distribution. A cohort of 115 COPD patients with mild to moderate disease was evaluated and potential correlations with clinical parameters (resting pulmonary function testing parameters (PFTs), severity of dyspnea, 6 minute walking test (6MWT), exacerbation rate, BODE index and St. George Respiratory Questionnaire) were investigated for four different emphysema distributions: core/peel and upper/lower predominance.(de Torres et al., 2011) Once again the impact of emphysema distribution on DH was not investigated.

In conclusion, data on published literature regarding potential correlations between emphysema distribution and physiologic and clinical parameters in COPD patients are scarce. Although there is some evidence that the site of parenchymal destruction is associated with resting pulmonary function variables, severity of dyspnea, 6MWT distance and quality of life in patients with alpha1 deficiency and in COPD patients with moderate to severe disease, no study has yet evaluated emphysema distribution's impact on DH and maximum exercise testing parameters. Furthermore, the published studies have adopted various techniques to characterize emphysema distribution, while some of them were conducted in non-COPD patients with emphysema, so results are not easy to compare.

Against his background we conducted a retrospective nested case-control study in order to identify:

a) the differences in the degree of DH occurring during maximum cardiopulmonary exercise testing (CPET) between COPD patients with heterogeneous and matched COPD patients with homogeneous emphysema,

b) the differences in maximal CPET parameters between COPD patients with heterogeneous and matched COPD patients with homogeneous emphysema and

c) the associations between emphysema distribution and CPET parameters in the two patient groups.

III. MATERIAL AND METHODS

A. Study population

Prospectively collected data on COPD outpatients who were assessed at the Respiratory Biomedical Research Unit of Royal Brompton Hospital between June 2009, and August, 2013 for potential eligibility to undergo a bronchoscopic LVR procedure, were retrospectively analyzed. Data on full lung function measurements, thoracic high resolution computed tomography (HRCT) and breath by breath data from maximum cycling CPET with inspiratory maneuvers were extracted from the hospital's records. The COPD patients were in stable clinical condition and were under treatment with various combinations of β_2-agonists, anticholinergic drugs and inhaled corticosteroids, according to guidelines. All patients gave their informed consent for their initial participation in the studies.(Shah et al., 2013; S. J. Clark et al., 2014; Davey et al., 2014) Corresponding identification numbers for all clinical trials are included in the Appendix.

B. Study measurements

Pulmonary Function Testing

Spirometry, gas transfer and lung volumes measurement by body plythesmography were conducted using a Compact Lab System (Jaeger, Hoechberg, Germany). FEV_1, FVC, FEV_1/FVC ratio, TLC, Functional Residual Capacity (FRC), RV, RV/TLC ratio, Carbon Monoxide Diffusion Capacity (TLCO) and KCO were recorded for each patient. Arterialized capillary blood samples were used to measure arterial PaO_2 and arterial $PaCO_2$. Arterialized capillary blood sampling is carried out routinely by clinical

physiologists in Royal Brompton Hospital and is better tolerated than an arterial puncture, while giving equivalent results.(Zavorsky, Cao, Mayo, Gabbay, & Murias, 2007)

The European Coal and Steel Community predicted values were used for lung function measurements (Quanjer et al., 1993) and the values of carbon monoxide diffusion capacity and transfer coefficient were adjusted for haemoglobin concentration (TLCOc and KCOc correspondingly).(E. H. Clark, Woods, & Hughes, 1978) All PFT values which were used, were measured prior to any bronchoscopic intervention and within a 6-month interval from both the HRCT and the maximum CPET.

HRCT acquisition and interpretation

Imaging was performed for clinical indications on 4-slice multidetector CT (Volume Zoom, Siemens, Erlangen, Germany), or 64-slice CT (Somatom Sensation 64, Siemens, Erlangen, Germany). Images were either acquired at 10-mm intervals (4-slice CT) or using a volumetric acquisition (64-slice CT) in a supine position from the lung apices to the bases at full inspiration without the use of intravenous contrast. Images were reconstructed at thin section width (1.0mm to 1.5mm) using a high spatial resolution algorithm and reviewed on a workstation at appropriate window settings for viewing the lung parenchyma (window centre = −500HU; window width = 1500HU).

Images were transferred to a post-processing workstation (Leonardo, Siemens) and quantitative lung density analysis was performed using the Pulmo CT program (Siemens, Version No.), which automatically segments the lung and calculates pixel attenuation coefficients as previously described (Gierada et al., 2001) with a minimum segmentation threshold of -1024HU. (Figure 1) Three representative slices of the lungs were analysed: (a) at the level where the top of the aortic arch just appears; (b) at the level of the carina,

where clear separation of the right and left main bronchi just becomes visible; and (c) at the level where neither diaphragm and nor abdominal viscera are visible (Figure 1).

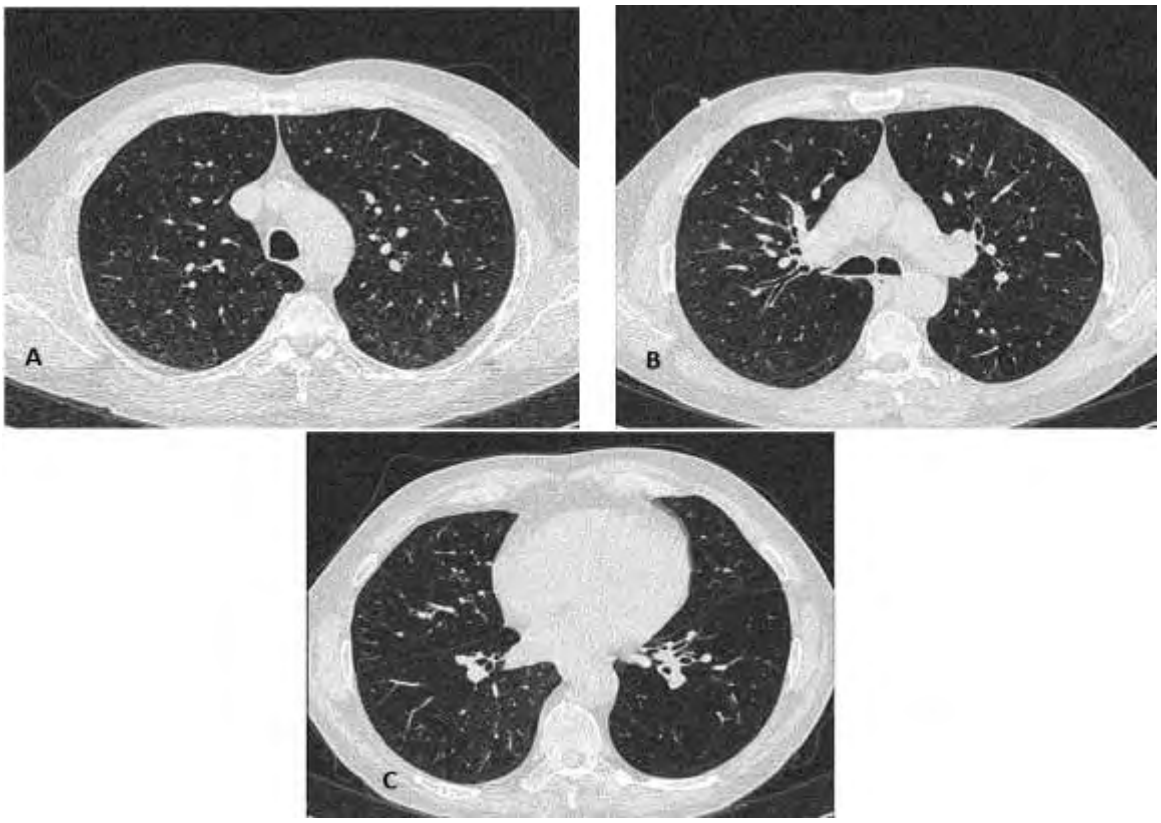

Figure 1. *A) Upper slice (at the level where the top of the aortic arch just appears), B) Middle slice (at the level of the carina, where clear separation of the right and left main bronchi just becomes visible) and C) Lower slice (at the level where neither diaphragm and nor abdominal viscera are visible)*

At each level, the program provides a total emphysema index, that is, the percentage of whole lung with attenuation values below a threshold of -900 HU, as well as a severe emphysema index, defined as percentage of whole lung with attenuation values below a threshold of -950 HU.(Gevenois, de Maertelaer, De Vuyst, Zanen, & Yernault, 1995; Gietema et al., 2011; Wang et al., 2013) An alternative threshold for emphysema definition of -960 HU has also previously been reported and we included this threshold as an additional quantitative parameter (Gierada et al., 1997) (Figure 2).

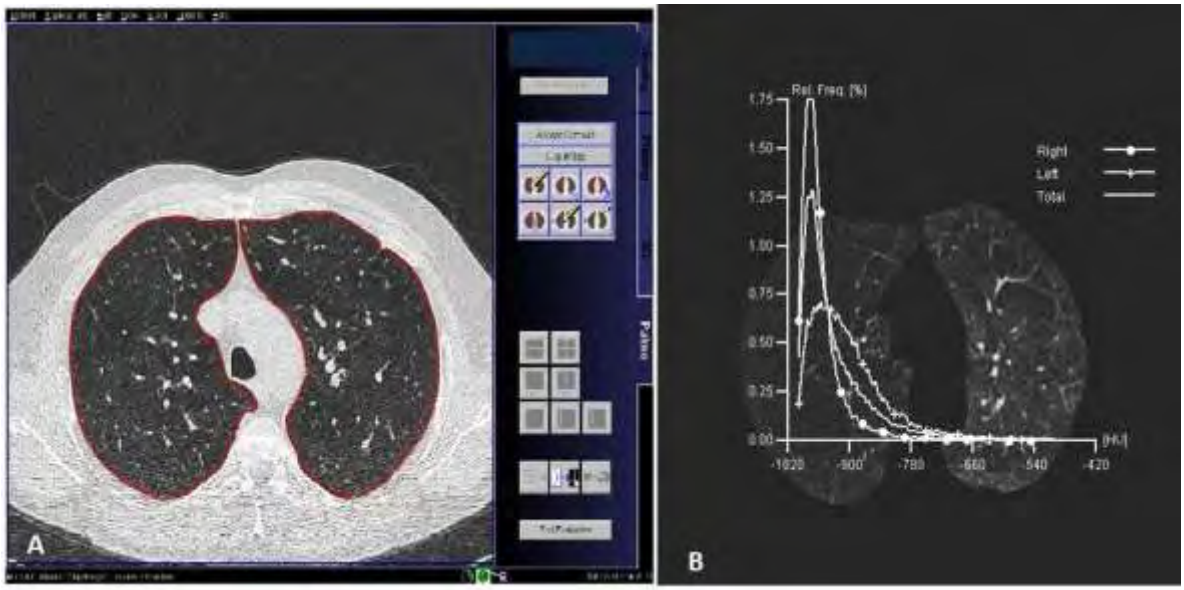

Figure 2. *A) Upper slice transferred to the post-processing workstation, where quantitative lung density analysis was performed using the Pulmo CT program. B) Histogram of distribution of lung attenuation values, measured in HU in the upper slice for several potential emphysema thresholds.*

To enable us to classify subjects as having either homogeneous or heterogeneous emphysema, we defined heterogeneous emphysema as a difference of >25% between the highest and lowest quantitative emphysema scores obtained, based on previous precedents of visual analysis.(National Emphysema Treatment Trial Research Group, 2001)

Maximum CPET

All patients performed an incremental symptom-limited CPET on a cycle ergometer (Jaeger Ergoline 800), under continuous monitoring of pulse oximetry (SaO_2), heart rate (HR), and a 12-lead electrocardiogram. The test consisted of 3 minutes of rest, 3 minutes of unloaded pedaling at 50-60 rpm, and then a ramp protocol with work rate (WR) increasing either 5 or 10 watts/minute, followed by 2 minutes of recovery.(American

Thoracic Society & American College of Chest Physicians, 2003) Severity of dyspnea was assessed using the 12 point modified Borg dyspnea scale, which is a linear, Likert type scale (see Appendix) that evaluates the subjective feeling of exertional dyspnea. Borg scale was originally a 21 point category scale for measuring perceived exertion during exercise,(Borg, 1982) but it was later modified to a 12 point scale and was adapted to estimate breathlessness.(Burdon, Juniper, Killian, Hargreave, & Campbell, 1982)

Gas exchange values and exercise parameters were collected breath-by-breath, using a Jaeger Oxycon system,(Beaver, Wasserman, & Whipp, 1986; Wasserman, 2005) allowing measurement of: respiratory rate (RR), Vt, oxygen uptake (VO_2), carbon dioxide production (VCO_2), end-tidal oxygen ($PETO_2$) and end-tidal carbon dioxide ($PETCO_2$). The anaerobic threshold (AT), oxygen pulse (VO_2/HR), respiratory exchange ratio (RER), minute ventilation (V_E) and the ventilator equivalent for carbon dioxide at peak VO_2 (V_E/VCO_2@VO_2 peak) were also calculated, as previously described.(Wasserman, 2005)

Inspiratory maneuvers

Each patient performed a total of four inspiratory maneuvers at 0, 1, 2, and 3 minutes of rest, in order IC to be measured, as previously described (Guenette et al., 2013) and resting IC (rIC) was calculated by averaging these values. To increase accuracy, a minimum of 4 stable breaths were conducted prior each inspiratory maneuver and volume was continuously monitored. This way the absolute volume of each IC could be accounted for any potential alterations of the EELV.(Guenette et al., 2013) Peak IC (pIC) was calculated by another inspiratory maneuver which was conducted during the last 30 seconds of peak exercise (Figure 3). This technique was selected to assess hyperinflation and changes in EELV during exercise, as previous data indicate its high reliability and reproducibility

during rest and incremental cycling exercise in COPD patients.(Yan, Kaminski, & Sliwinski, 1997; O'Donnell et al., 2009)

The change of IC from rest to peak exercise (ΔIC) was utilized as a measure of DH and was calculated as rIC-pIC. For every patient, ΔIC was expressed as a % percentage of rIC, that is: ΔIC%=(ΔIC/rIC) X100%. All exercise tests were performed before any bronchoscopic intervention took place and without oxygen supplementation.

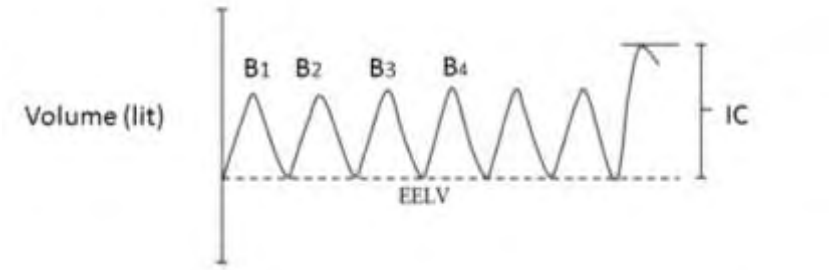

Figure 3. *Measurement of IC during an inspiratory maneuver. B_1, B_2, B_3, B_4,….correspond to number of breaths during tidal breathing and before the conduction of the IC maneuver*

Statistical analysis

Statistical analysis was conducted utilizing the PASW (Predictive Analytics Software by SPSS Inc®) version 19 for Windows 2008. Distribution of values was assessed using the Shapiro-Wilk test of normality; continuous variables are described as mean±1 standard deviation or as median (minimum-maximum), accordingly. Group comparisons in PFTs, DH and exercise parameters were conducted utilizing either the independent samples Student's t-test or the Mann-Whitney test, depending on the normality of their distribution. Pearson *r* or Spearman *rho* were used to describe parametric and non-parametric correlations between emphysema distribution indices, DH measures, and exercise

parameters. Scatterplots were utilized to graphically describe the correlations between measures of DH and CPET parameters. Level of $p<0.05$ was considered significant.

IV. RESULTS

Study population

A total of 136 COPD patients of various severity were assessed for potential eligibility to undergo a bronchoscopic or surgical LVR procedure between April 2002 and August 2013. From this initial population, 38 patients were excluded, because they had undergone a thorax CT scan which could not be used for further analysis (images were neither acquired at 10-mm intervals nor using a volumetric acquisition). From the remaining 98 patients, another 34 were excluded for any of the following reasons: a) they had undergone an endurance and not an incremental CPET, b) they had undergone an incremental CPET, but it was submaximal and c) exercise data could not be fully retrieved due to an older software version used. The remaining 64 COPD patients, who fulfilled the enrolment criteria and constituted the final study population, had been all assessed at the Respiratory Biomedical Research Unit of Royal Brompton Hospital between June 2009, and August, 2013. (Figure 4)

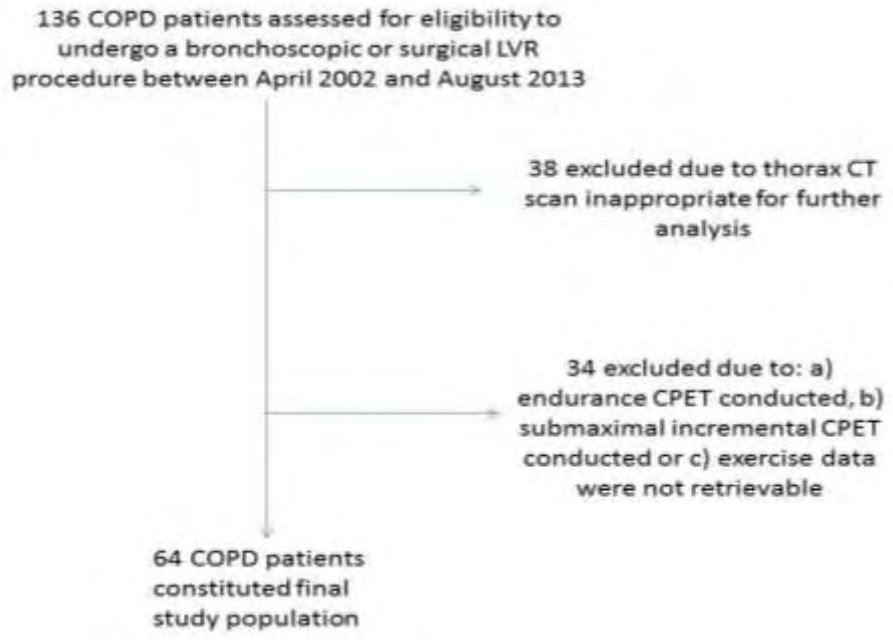

Figure 4. *Study flowchart*

Baseline characteristics

The baseline characteristics of the final study population are presented in Table 2. When the -950 HU emphysema threshold was applied, 50 patients (78.1%) presented with heterogeneous and 14 patients (21.9%) with homogeneous emphysema (group Het and group Hom correspondingly).

Table 2. Demographic characteristics for the whole study population

Characteristic	**Study population (N=64)**
Age	61.3±7.2
Gender (%)	
-male	62.5
-female	37.5
BMI (kg/m^2)	24.3±4.3
FEV_1 %predicted	31.5±11.2
FEV_1/FVC	28.6±6.9
TLC %predicted	136.8±15.3
RV %predicted	230.3±42.4
RV/TLC (%)	61.4±7.9
FRC %predicted	185.6±35.9
TLCOc %predicted	34±10
KCOc %predicted	45.1±12
PaO_2 (kPa)	9.6±1.2
$PaCO_2$ (kPa)	4.8±0.8

BMI: Body Mass Index; FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; TLC: Total Lung Capacity; RV: Residual Volume; FRC: Functional Residual Capacity; TLCOc: Carbon Dioxide Diffusion Capacity; KCO: Carbon Dioxide Diffusion

Coefficient; PaO_2: arterial Oxygen Partial Pressure; $PaCO_2$: arterial Carbon Dioxide Partial Pressure

An initial attempt for patients in Hom group to match the same number of patients in Het group (1:1 matching) for age, FEV_1 and $TLCO_c$ was made. However, the two patient groups (Hom and Het) were found to be matched not only regarding these three selected variables, but also regarding gender, body mass index (BMI), resting PFTs and gas transfer parameters, which resulted to an approximate 1:3 matching. The number of patients in the two groups (Hom and Het) was identical when the alternative -960 HU emphysema threshold was applied. The baseline demographic characteristics of the two groups are presented in Table 3.

Table 3. Baseline characteristics of the two study groups

Characteristic	**Group Het (n_1=50)**	**Group Hom (n_2=14)**	***p***
Age	60.9±7.5	62.5±5.9	0.471
Gender (%)			
-male	62.7	61.5	0.936
-female	37.3	38.5	
BMI (kg/m^2)	24±4.5	25.6±3.6	0.243
FEV_1 %predicted	32.4±11.4	28.1±10.3	0.213
FEV_1/FVC	29.1±7	26.5±6.4	0.216
TLC %predicted	137±16.4	132.4±9.4	0.198
RV %predicted	232.8±44.6	220.7±32	0.365
RV/TLC (%)	61.6±8.5	60.8±5.2	0.757
FRC %predicted	189.9±31.5	168.8±47.4	0.059
TLCOc %predicted	34.1±10	33.3±11.5	0.867
KCOc %predicted	45.8±12	40±12.1	0.300
PaO_2 (kPa)	9.6±1.3	9.2±1	0.527
$PaCO_2$ (kPa)	4.8±0.7	5.1±1.5	0.398

BMI: Body Mass Index; FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; TLC: Total Lung Capacity; RV: Residual Volume; FRC: Functional Residual Capacity; TLCOc: Carbon Dioxide Diffusion Capacity; KCOc: Carbon Dioxide Diffusion Coefficient; PaO^2: arterial Oxygen Partial Pressure; $PaCO_2$: arterial Carbon Dioxide Partial Pressure

Exercise parameters

Exercise parameters for the whole population are presented in Table 4, while group comparisons are presented in Table 5. Although both dyspnea and muscle endurance were evaluated during exercise, all patients stopped because of dyspnea and the degree of breathlessness did not differ between groups. Only 15 patients (11 from Het group and 4 from Hom group) reached AT during maximal CPET, thus corresponding exercise variables (AT %predicted, Ventilatory Equivalent for carbon dioxide at AT (V_E/VCO_2@AT), End Tidal Carbon Dioxide at AT ($PETCO_2$@AT) and Oxygen Pulse at AT (VO_2/HR@AT)) were not further analyzed. No patient presented with any symptom or sign such as dizziness, chest pain suggestive of ischemia or severe arrhythmias, indicating that exercise testing should be terminated before symptom limitation, according to guidelines.(American Thoracic Society & American College of Chest Physicians, 2003)

Patients in the Hom group displayed more DH during exercise, as ΔIC% was significantly higher among Hom group compared to Het group; 39.8% vs 31.2% (p=0.031). No other differences were noted between the groups regarding CPET parameters. No other differences were noted between the groups regarding CPET parameters (Table 5 and Figure 5).

Table 4. Exercise parameters for the whole study population

Exercise parameter	**Study population (N=64)**
rIC (lit)	2.2±0.7
pIC (lit)	1.5±0.5
ΔIC %	32.9±12.9
rBorg	1(0-5)
pBorg	7(4-10)
ΔBorg	4.9±2.2
Peak V_E (lit)	34(15-84)
Peak Vt (lit)	1.1(0.53-2.33)
Peak VO_2 (ml/kg/min)	13.1(7.8-26.2)
Peak VO_2 %predicted	50.4±15.5
Peak WR %predicted	26(5-73)
Peak VCO_2 (ml)	820.9(361.7-2023.4)
RER	0.9(0.4-1.5)
Peak HR %predicted	75.9±13.7
Peak $PETO_2$ (kPa)	15±1.1
Peak $PETCO_2$ (kPa)	4.6(2.3-8.3)
Peak VE/VCO_2	39.6(21-72.2)
Peak VO_2/HR %predicted	67.2±20
RR (breaths/min)	31.5(18-56)
$rSPO_2$ (%)	95(88-99)
$pSPO_2$ (%)	89(79-98)
ΔSPO_2	6±3.3

rIC: rest Inspiratory Capacity; pIC: peak Inspiratory Capacity; rBorg: rest Borg scale score; pBorg: peak Borg scale score; V_E: Minute ventilation; Vt: Tidal Volume; VO_2: Oxygen Consumption; WR: Work Rate; VCO_2: Carbon Dioxide Production; RER: Respiratory Exchange Ratio; HR: Heart Rate; $PETO_2$: End Expiratory Oxygen partial pressure; $PETCO_2$: End Expiratory Carbon Dioxide partial pressure; V_E/VCO_2: Ventilatory Equivalent for Carbon Dioxide; VO_2/HR: Oxygen Pulse; $rSPO_2$: rest arterial Oxygen Saturation; $pSPO_2$: peak arterial Oxygen Saturation

Table 5. Comparison of exercise parameters between patients with heterogeneous and homogeneous emphysema

Exercise parameter	**Group Het (n_1=50)**	**Group Hom (n_2=14)**	**p**
rIC (lit)	2.2±0.7	2.2±0.5	0.932
pIC (lit)	1.5±0.5	1.3±0.3	0.240
ΔIC %	31.2±13	39.8±9.8	***0.031***
rBorg	1(0-5)	2(0-2)	0.441
pBorg	7(4-10)	7(5-7)	0.807
ΔBorg	5(1-9)	5(3-7)	0.852
Peak V_E (lit)	34(15-47)	32(18-84)	0.593
Peak Vt (lit)	1.1(0.5-2.3)	1(0.7-1.4)	0.739
Peak VO_2 (ml/kg/min)	13.3(7.9-26.2)	12.5(7.8-26)	0.349
Peak VO_2 %predicted	49(13-99)	44(14-67)	0.246
Peak WR %predicted	26(5-73)	34(12-59)	0.361
Peak VCO_2 (ml)	780.6(404-2023.4)	934.6(361-1025)	0.944
RER	0.9(0.4-1.3)	0.9(0.4-1.5)	0.662
Peak HR %predicted	75.5(42-106)	75.5(65-86)	0.802
Peak $PETO_2$ (kPa)	14.9(13-18)	14.9(11.4-16)	0.441
Peak $PETCO_2$ (kPa)	4.7(2.3-6.7)	4.6(3.6-8.3)	0.687
Peak V_E/VCO_2	39.4(26.9-72.2)	41.6(21-48.3)	0.834
Peak VO_2/HR %predicted	66.6(14.4-112.3)	59(20.4-82)	0.131
RR (breaths/min)	32.9±8.9	31.2±9.4	0.545
$rSPO_2$ (%)	94.5(88-99)	96(91-98)	0.323
$pSPO_2$ (%)	89(79-98)	89(80-95)	0.869
ΔSPO_2	6(0-12)	6.5(3-11)	0.674

rIC: rest Inspiratory Capacity; pIC: peak Inspiratory Capacity; rBorg: rest Borg scale score; pBorg: peak Borg scale score; V_E: Minute ventilation; Vt: Tidal Volume; VO_2: Oxygen Consumption; WR: Work Rate; VCO_2: Carbon Dioxide Production; RER: Respiratory Exchange Ratio; HR: Heart Rate; $PETO_2$: End Expiratory Oxygen partial pressure; $PETCO_2$: End Expiratory Carbon Dioxide partial pressure; VE/VCO_2: Ventilatory Equivalent for Carbon Dioxide; VO_2/HR: Oxygen Pulse; $rSPO_2$: rest arterial Oxygen Saturation; $pSPO_2$: peak arterial Oxygen Saturation

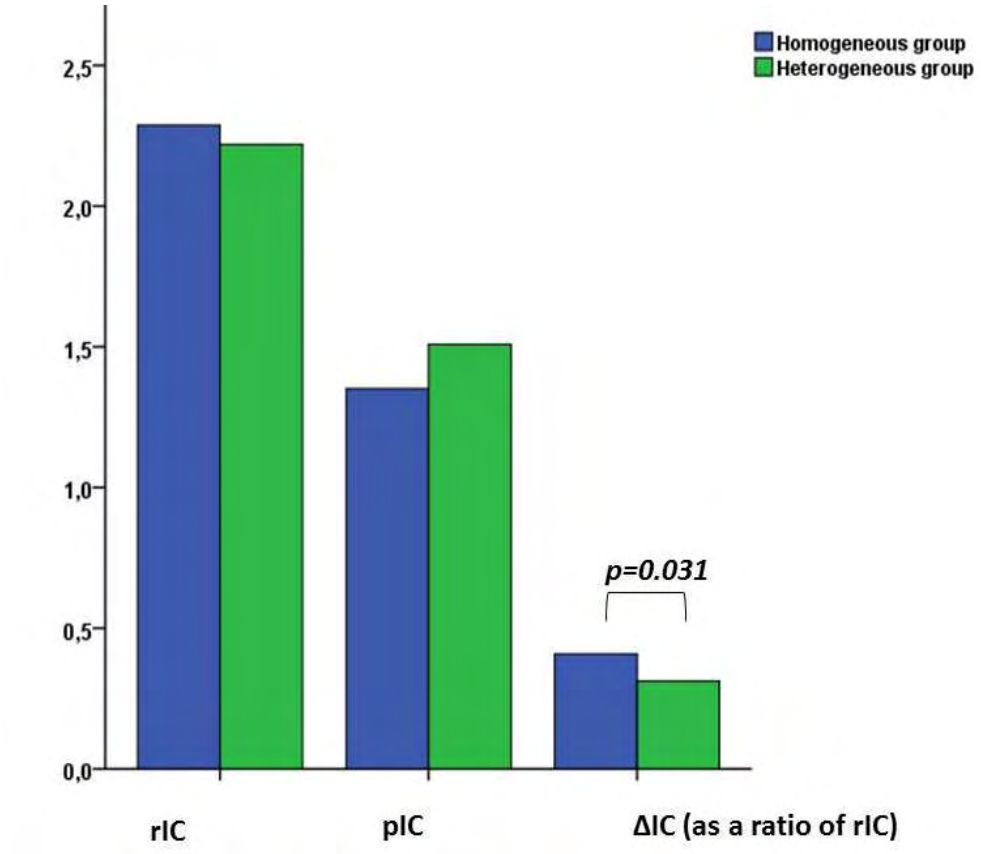

Figure 5. *Differences between groups in rIC, pIC and absolute ΔIC.*

Emphysema distribution as a continuous variable

Alternatively, emphysema was treated as a continuous variable and specifically as a ratio of average emphysema score of the upper and middle slice versus average emphysema score of the lower slice (UM/L) for both 950 and 960 emphysema thresholds. A high ratio therefore represents heterogeneous emphysema with upper lobe predominance.

Table 5 presents the non-parametric correlations between UM/L ratio, ΔIC% and CPET parameters. The UM/L ratio established a weak, inverse but significant correlation to ΔIC% for both -950 and -960 emphysema thresholds (Spearman rho=-0.264, p=0.049; Spearman rho=-0.246, p=0.049, correspondingly). Moreover, peak VO_2 %predicted, peak

VO_2/HR %predicted and peak RR were all positively correlated to UM/L ratio. (Table 6 and Figures 6-13)

Table 6. Correlations between emphysema distribution and exercise parameters, for both emphysema thresholds

Exercise parameter	950UM/L	960UM/L
ΔIC %	-0.264*	-0.246*
rBorg	-0.018	0.016
pBorg	0.096	0.068
ΔBorg	0.078	0.030
Peak V_E (lit)	0.186	0.040
Peak Vt (lit)	0.025	0.053
Peak VO_2 (ml/kg/min)	0.050	0.033
Peak VO_2 %predicted	0.340**	0.341**
Peak WR %predicted	0.087	0.040
Peak VCO_2 (ml)	0.130	0.128
RER	0.075	0.110
Peak HR %predicted	-0.074	-0.086
Peak $PETO_2$ (kPa)	0.193	0.197
Peak $PETCO_2$ (kPa)	-0.097	-0.109
Peak V_E/VCO_2	-0.006	0.010
Peak VO_2/HR %predicted	0.398**	0.390**
Peak RR (breaths/min)	0.300*	0.266*
rSPO_2 (%)	0.046	0.030
pSPO_2 (%)	0.079	0.069
ΔSPO_2	-0.099	-0.091

IC: Inspiratory Capacity; rBorg: rest Borg scale score; pBorg: peak Borg scale score; V_E: Minute ventilation; Vt: Tidal Volume; VO_2: Oxygen Consumption; WR: Work Rate; VCO_2: Carbon Dioxide Production; RER: Respiratory Exchange Ratio; HR: Heart Rate; $PETO_2$: End Expiratory Oxygen partial pressure; $PETCO_2$: End Expiratory Carbon Dioxide partial pressure; V_E/VCO_2: Ventilatory Equivalent for Carbon Dioxide; VO_2/HR: Oxygen Pulse; rSPO_2: rest arterial Oxygen Saturation; pSPO_2: peak arterial Oxygen Saturation
* Significant correlation at 0.05 level; **Significant correlation at 0.01 level

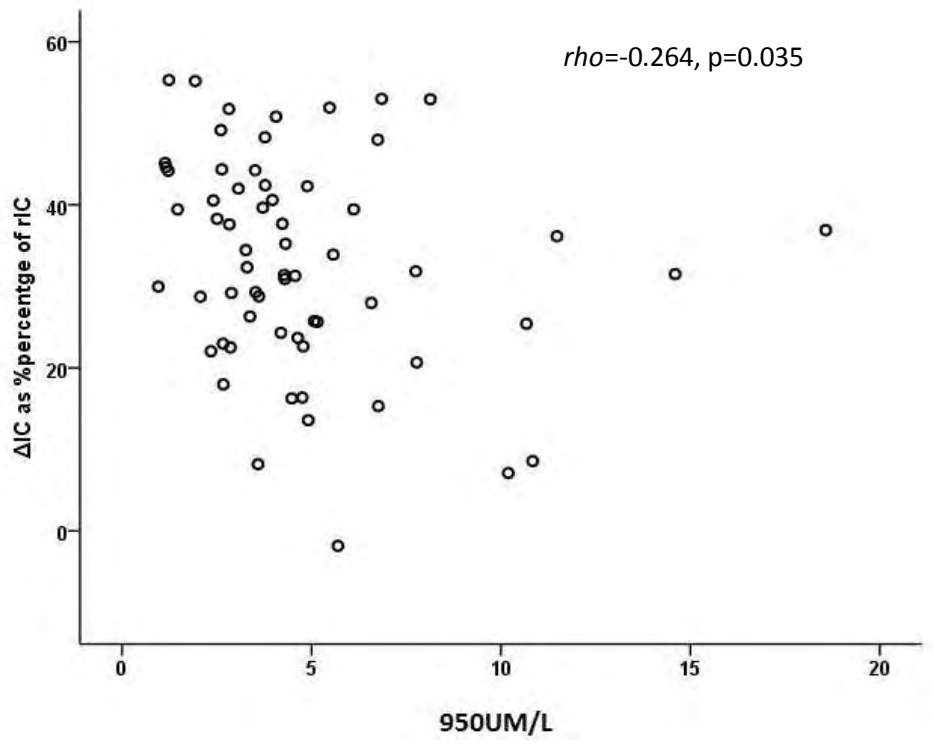

Figure 6. *Correlation between 950UM/L ratio and ΔIC %*

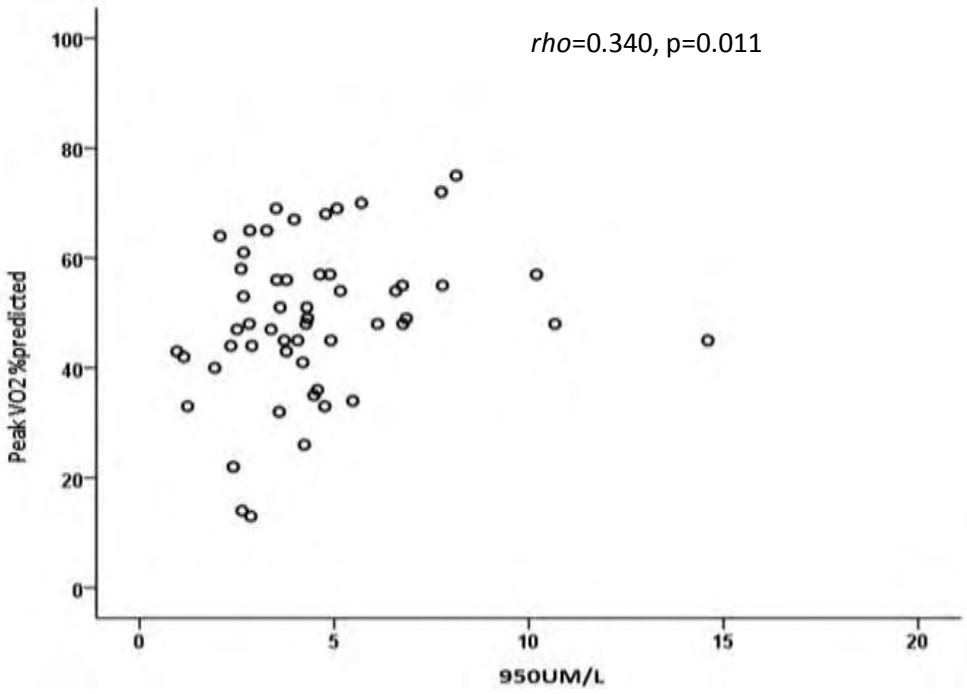

Figure 7. *Correlation between 950UM/L ratio and Peak VO_2 %predicted*

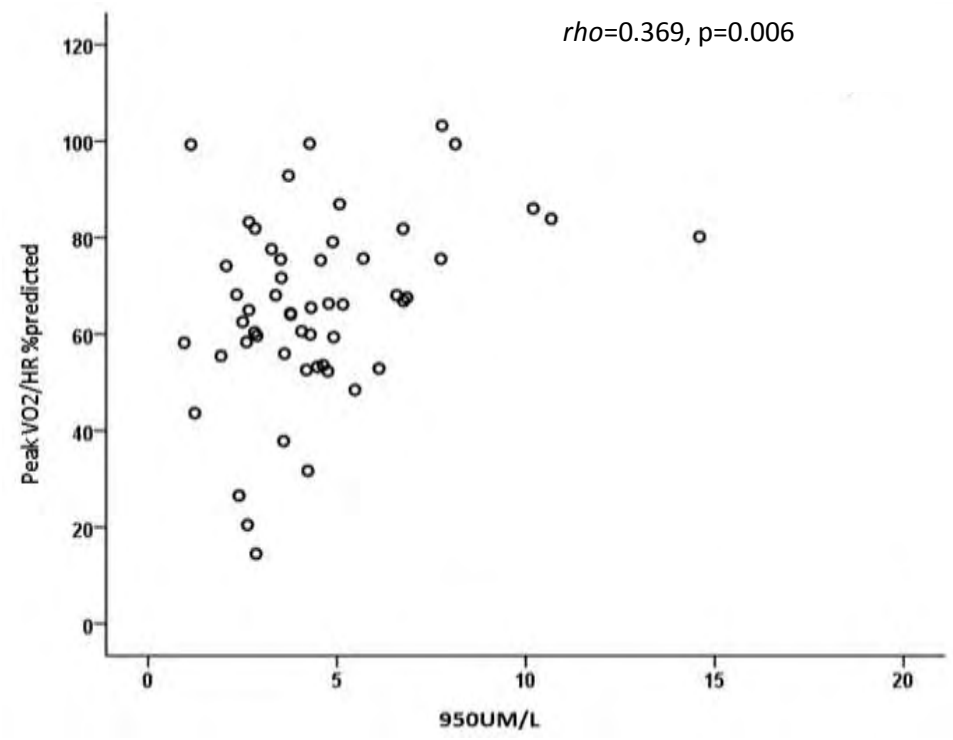

Figure 8. *Correlation between 950UM/L ratio and Peak VO_2/HR %predicted*

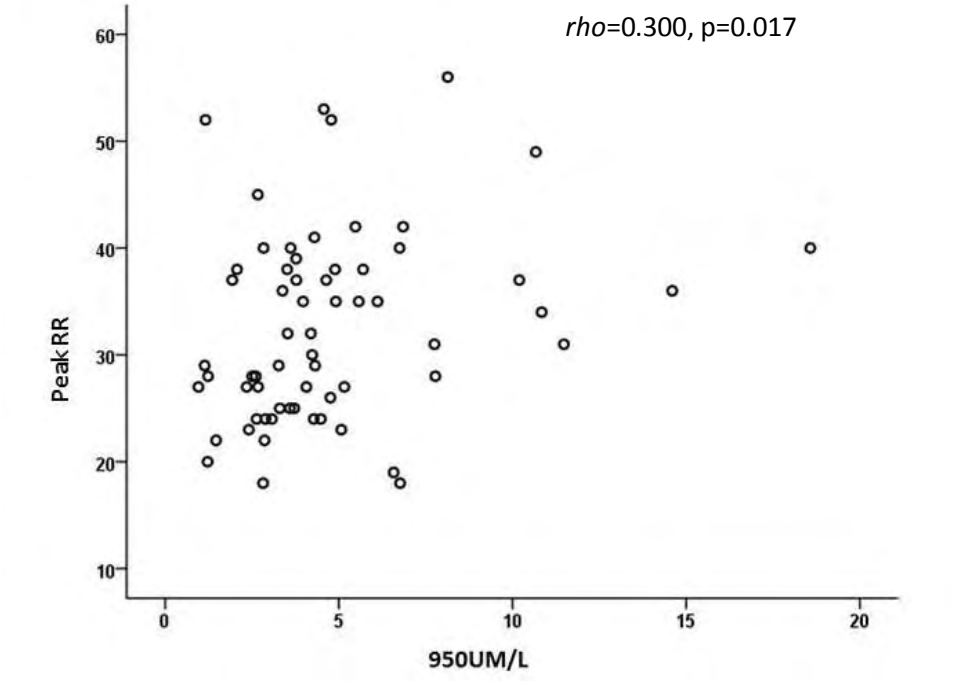

Figure 9. *Correlation between 950UM/L ratio and Peak RR*

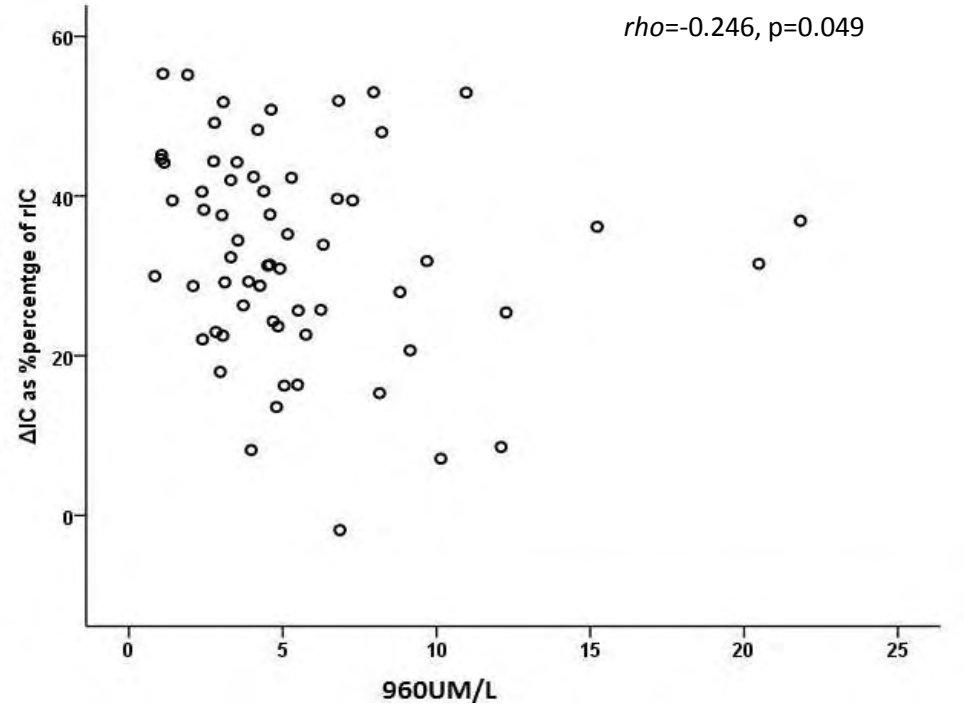

Figure 10. *Correlation between 960UM/L ratio and ΔIC %percentage of rIC*

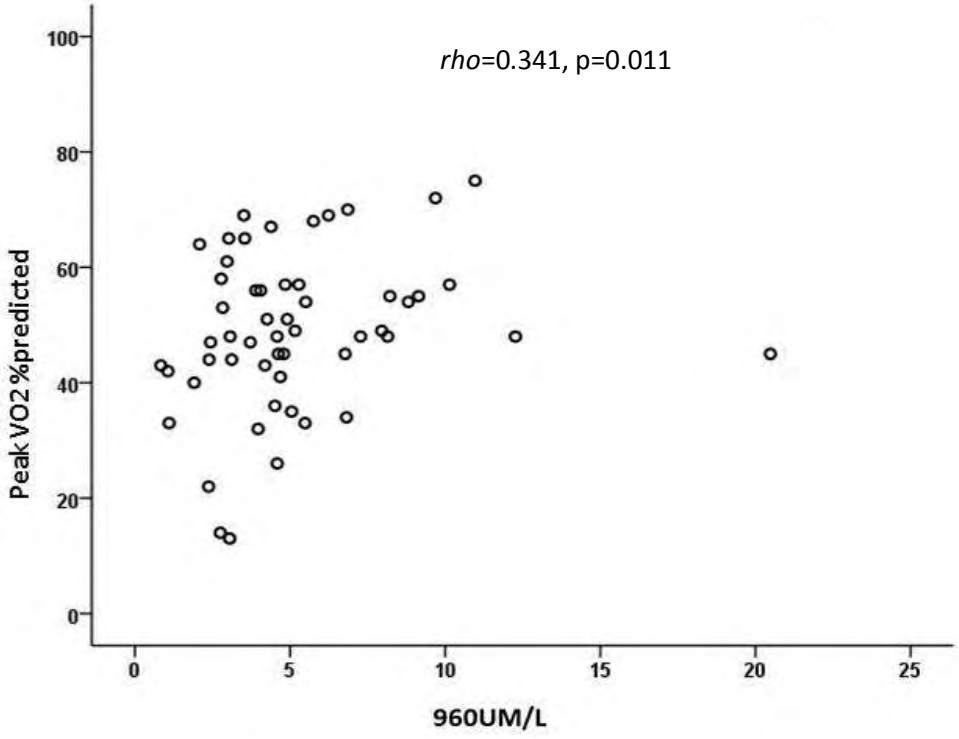

Figure 11. *Correlation between 960UM/L and Peak VO_2 %predicted*

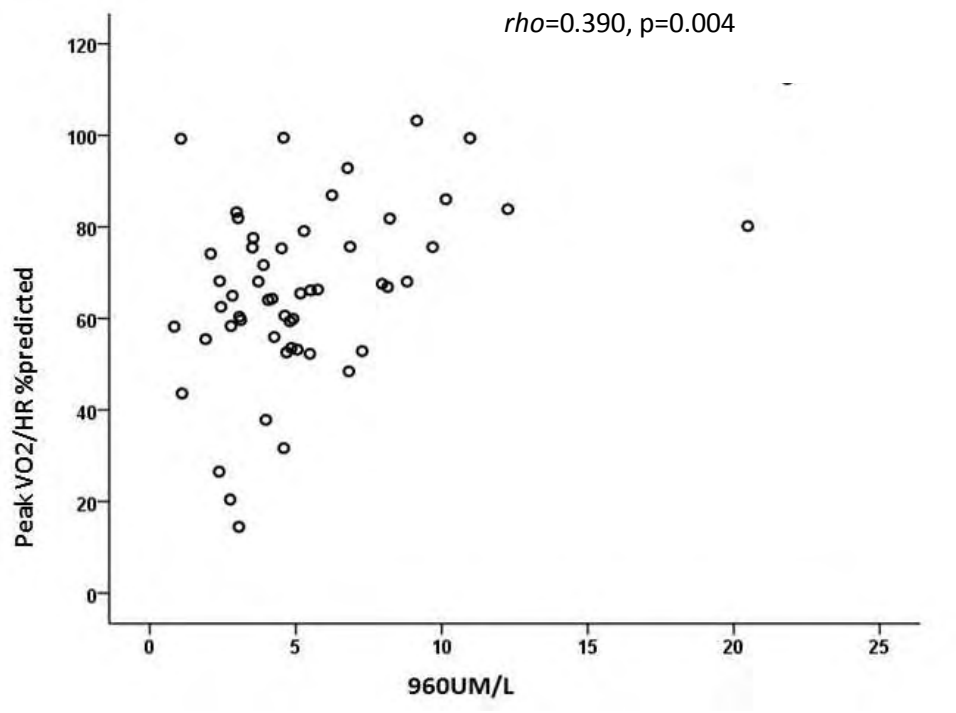

Figure 12. *Correlation between 960UM/L ratio and Peak VO_2/HR %predicted*

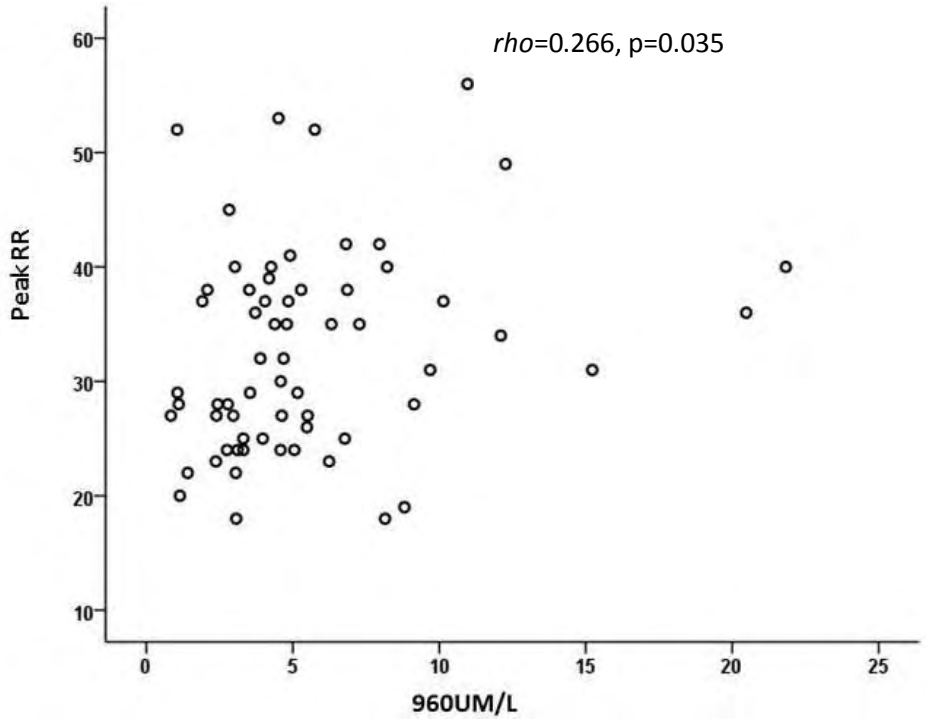

Figure 13. *Correlation between 960UM/L ratio and Peak RR*

V. DISCUSSION

This retrospective nested case-control study aimed to investigate whether emphysema distribution has any impact on DH and exercise parameters during a maximum CPET, for the first time in literature. Patients with homogeneous emphysema tended to hyperinflate more compared to the ones with heterogeneous emphysema, although no differences were noted regarding exercise variables, between the groups. Furthermore, emphysema heterogeneity and particularly upper lobe predominance correlated inversely with DH, and positively with peak oxygen consumption, peak oxygen pulse and peak RR.

Emphysema distribution varies significantly among individuals and possibly represents the different pathogenetic patterns of the disease development.(Mair et al., 2009) Three different subtypes of emphysema have been recognized: a) centriacinar emphysema, which predominantly involves the upper lobes and is associated with long-standing cigarette smoking, b) panacinar emphysema, which mainly involves the lower lobes and is frequently found in patients with a1-deficiency and c) distal acinar emphysema, which tends to occur adjacent to the pleura or the fibrous septa.(Russi et al., 1999) These pathologic lesions are found in various combinations in each patient, comprising a heterogeneous or homogeneous emphysema pattern, as classified by CT imaging.(Weder et al., 1997; Russi et al., 1999) Mair et al (2009) indicated that emphysema distribution is associated with several clinical features, such as FEV_1, BMI, BODE index and Saint George Respiratory Questionnaire score; however, these associations were most evident among patients with core versus rind predominant, rather than upper versus lower predominant emphysema. Moreover, the presence of heterogeneity has been repeatedly associated with improved outcomes and increased survival after a LVR procedure.(McKenna et al., 1997; Sanchez, Kucharczuk, Su, Kaiser, & Cooper, 2010) Although the theoretical background of these interventions is the restoration of lung elastic

recoil and the improvement of lung mechanics, the impact of emphysema distribution on DH has never been previously assessed.

Both pathologic hallmarks of COPD, airway inflammation and parenchymal destruction, contribute to the development of DH.(Puente-Maestu & Stringer, 2006) During exercise, the increased airway resistance and the decreased elastic recoil pressure, result in increased time constants for alveolar units, so as the RR and expiratory flow increase, the expiratory time available for exhalation becomes insufficient.(O'Donnell & Laveneziana, 2006; Gagnon et al., 2014) Given the variety of distribution of parenchymal destruction among COPD patients, it is possible that its general pattern might have an impact on lung deflation. In our study, patients with heterogeneous emphysema, that is with unequally distributed parenchymal damage, presented with significantly less DH during maximal exercise, compared to the ones with homogeneous one. In patients with heterogeneous emphysema, lung areas with distinct destruction coexist with areas where lung parenchyma is well preserved.(Russi et al., 1999) The presence of areas with severe emphysematous destruction could be accompanied with the compression of adjacent lung tissue, a phenomenon less evident among patients with homogeneous emphysema. One could hypothesize that this compression poses a mechanical barrier for the further increase of end expiratory lung volume, resulting to less DH during maximal exercise, but this is a hypothesis that needs to be further investigated.

Interestingly, no CPET parameter differed significantly between patients of Het and Hom group. It is well established that medical or other interventions targeting on lung hyperinflation improve exercise tolerance among COPD patients.(O'Donnell, Lam, & Webb, 1998; Maltais et al., 2005; Hopkinson et al., 2005) Tzani et al (2011) reported that DH was associated with increased exertional dyspnea and reduced maximum exercise capacity in a cohort of COPD patients; however a relatively high value of end expiratory

lung volume (≥75% TLC) was used as a threshold for group categorization. In another study ΔIC was associated with exercise desaturation; nevertheless, this study utilized a submaximal exercise testing and not maximal CPET.(Zafar, Tsuang, Lach, Eschenbacher, & Panos, 2013) The relatively small size of Hom group, and the significant, but rather small (approximately 8.5%) difference in ΔIC% between the groups, might justify our results. Nevertheless, apart from these potential limitations, our study has compared the exercise capacity in two COPD groups which differed in the distribution of parenchymal involvement, so exercise performance might be affected, apart from DH, by other potential pathological or mechanical factors which could be distinct in these two populations and remain to be identified.

When emphysema distribution was treated as a continuous variable, significant correlations were established with several CPET parameters. The higher the emphysema heterogeneity with upper lobe predominance, as manifested by increased UM/L ratio, the lower the ΔIC%, and the higher the peak O_2 consumption and the peak oxygen pulse. Lung hyperinflation is the most probable cause of this circulatory impairment during exercise, as it has been previously established.(Miller et al., 2005; Vassaux et al., 2008; Tzani et al., 2011) The use of respiratory muscles during active expiration in combination with DH which produces an intrinsic PEEP could reduce venous return and right ventricular preload.(Puente-Maestu & Stringer, 2006) Left ventricular afterload may also increase during exercise in COPD patients, since high intrathoracic pressure swings have to be generated to overcome the increased high elastic and resistive loads.(Montes de Oca et al., 1996; Gagnon et al., 2014) These combined effects of DH result to functional hypovolemia during exercise,(Vassaux et al., 2008) which may have an impact on stroke volume, as manifested in our study by its inverse association to oxygen pulse. Whether the unequal distribution of parenchymal destruction itself, as seen in heterogeneous emphysema,

compromise cardiac function less, compared to the homogeneous one, due to the potential compensatory effect of preserved lung areas and irrespectively from the degree of DH, is a hypothesis that remains to be tested. Another interesting finding regarding CPET parameters in this study is that peak RR is positively associated to emphysema heterogeneity, which indicates the development of a rapid swallow breathing pattern during exercise, among these COPD patients, possibly due to the presence of "compressed" lung.

Methodological issues

Although data were retrospectively analyzed, their prospective collection has minimized the general bias seen in this kind of studies. COPD patients who were included in the study were followed-up in a tertiary hospital and they were assessed for a LVR procedure, so results should be generalized in primary care COPD populations with some caution. This may also explain the high proportion of heterogeneous emphysema identified. The study is strengthened by the single center approach, which has minimized bias that could occur in multicenter cohorts, regarding different patient populations included and various measurement techniques applied. The nested case-control design allowed matching for other parameters which could potentially affect DH, such as resting lung function. Although the categorization of emphysema distribution was performed with the utilization of a well-established technique, the use of UM/L ratio as a continuous variable to describe upper-lobe predominance in sub analysis has not been reported previously and needs to be further validated; Nevertheless its correlation with parameters of exercise capacity and DH is in accordance with published literature,(Vassaux et al., 2008; Tzani et al., 2011) which strengthens the rationale of its use.

VI. CONCLUSIONS

In conclusion, this study indicated that patients with homogeneous emphysema hyperinflate significantly more during maximum exercise compared to the ones with heterogeneous emphysema. Upper lobe predominance was also associated with less DH and with a higher peak VO_2, peak VO_2/HR and peak RR; however no CPET parameter was found to be different between the groups, probably due to the significant but not vast difference in ΔIC% and the relatively small size of homogeneous group. Based on these findings, the primary null hypothesis is rejected, but the secondary null hypothesis is not.

Lung hyperinflation has been associated with adverse disease outcomes and thus, several medical treatments, particularly bronchodilator therapy and invasive interventions have targeted on its improvement.(Gagnon et al., 2014)(Puente-Maestu & Stringer, 2006)(Sanguinetti, 2014) However, apart from LVR procedures, almost no other therapeutic application has guided patient selection according to emphysema heterogeneity. This study strengthens the case that CT pattern of emphysema distribution should be taken under consideration in designing such interventional protocols and evaluating their outcome in the future, as it could be an important determinant of DH.

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APPENDIX

I. Identification (registry) numbers for the clinical trials whose participants were included in the current study

A) Bronchoscopic Intrabullous Autologous Blood Instillation (BIABI) for Emphysema clinical study

-Clinical Trials code number: NCT01727037

B) Lung Volume Reduction Coil for Treatment in Patients With Emphysema (RENEW) Study

-Clinical Trials code number: NCT01608490

C) Endobronchial Valves for Emphysema Palliation Trial (VENT)

-Clinical Trials code number: NCT00129584

D) Lung Volume Reduction Surgery (LVRS) study

-Clinical Trials code number: NCT00018525

II. The Modified Borg Dyspnea Scale (Burdon et al., 1982)

How would you rate your dyspnea right now?