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Original Article

Muscle Glucose Metabolism in Chronic Obstructive Pulmonary Disease Patients☆

Antonio Sancho-Muñoz,[a] Carlos Trampal,[d] Sergi Pascual,[a,b,c] Juana Martínez-Llorens,[a,b,c] Roberto Chalela,[a] Joaquim Gea,[a,b,c,*] Mauricio Orozco-Levi[a,b,c,e]

[a] *Servicio de Neumología, Hospital del Mar–IMIM, Barcelona, Spain*
[b] *Departamento de Ciencias Experimentales y de la Salud (CEXS), Universitat Pompeu Fabra, Barcelona, Spain*
[c] *Centro Radiológico Computarizado (CRC), Bunyola (Mallorca), Spain*
[d] *Centro Radiológico Computarizado (CRC), Barcelona, Spain*
[e] *Servicio de Neumología, Fundación Cardiovascular de Colombia, Bucaramanga, Colombia*

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ABSTRACT

Introduction: Muscle dysfunction is one of the most extensively studied manifestations of COPD. Metabolic changes in muscle are difficult to study in vivo, due to the lack of non-invasive techniques. Our aim was to evaluate metabolic activity simultaneously in various muscle groups in COPD patients.
Methods: Thirty-nine COPD patients and 21 controls with normal lung function, due to undergo computed axial and positron emission tomography for staging of localized lung lesions were included. After administration of 18-fluordeoxyglucose, images of 2 respiratory muscles (costal and crural diaphragm, and rectus abdominus) and 2 peripheral muscles (brachial biceps and quadriceps) were obtained, using the standard uptake value as the glucose metabolism index.
Results: Standard uptake value was higher in both portions of the diaphragm than in the other muscles of all subjects. Moreover, the crural diaphragm and rectus abdominus showed greater activity in COPD patients than in the controls (1.8±0.7 vs 1.4±0.8; and 0.78±0.2 vs 0.58±0.1; respectively, $P<.05$). A similar trend was observed with the quadriceps. In COPD patients, uptake in the two respiratory muscles and the quadriceps correlated directly with air trapping (r=0.388, 0.427 and 0.361, respectively, $P<.05$).
Conclusions: There is greater glucose uptake and metabolism in the human diaphragm compared to other muscles when the subject is at rest. Increased glucose metabolism in the respiratory muscles (with a similar trend in their quadriceps) of COPD patients is confirmed quantitatively, and is directly related to the mechanical loads confronted.

Utilización de glucosa en los músculos de pacientes con enfermedad pulmonar obstructiva crónica

Palabras clave:
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Enfermedad pulmonar obstructiva crónica
Tomografía por emisión de positrones
Diafragma
Cuádriceps

RESUMEN

Introducción: La disfunción muscular es una de las manifestaciones sistémicas más estudiadas en la EPOC. Las alteraciones metabólicas musculares son difíciles de estudiar in vivo, debido a la falta de técnicas no invasivas. El objetivo fue evaluar sincrónicamente la actividad metabólica de diferentes grupos musculares en pacientes con EPOC.
Métodos: Se incluyeron 39 pacientes y 21 controles (función pulmonar normal), candidatos a realización de tomografía axial computarizada y por emisión de positrones para estadificación de lesión pulmonar localizada. Tras infusión de 18-fluor-deoxi-glucosa, se captaron imágenes de 2 músculos respiratorios (porciones costal y crural del diafragma, y recto abdominal) y 2 músculos periféricos (cuádriceps y bíceps braquial), utilizando como índice de metabolismo glucídico el *standard uptake value.*

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* Corresponding author.
E-mail address: jgea@parcdesalutmar.cat (J. Gea).

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Resultados: Este índice fue superior en ambas porciones del diafragma comparado con el resto de los músculos en todos los sujetos. Además, el diafragma crural y el recto del abdomen mostraban mayor actividad en los pacientes con EPOC que en los controles (1,8 ± 0,7 vs. 1,4 ± 0,8; y 0,78 ± 0,2 vs. 0,58 ± 0,1; respectivamente; p < 0,05). El cuádriceps mostraba una tendencia similar. En los pacientes con EPOC los niveles de captación de ambos músculos respiratorios y del cuádriceps se correlacionaron directamente con el atrapamiento aéreo (r = 0,388; 0,427 y 0,361, respectivamente; p < 0,05).
Conclusiones: Existe mayor nivel de captación-utilización de glucosa en el diafragma humano respecto de otros músculos en respiración tranquila. Se confirma cuantitativamente que los pacientes con EPOC tienen incrementado el metabolismo glucídico de sus músculos respiratorios (con tendencia similar para el cuádriceps), en relación directa con las cargas mecánicas que afrontan.

Introduction

Chronic obstructive pulmonary disease (COPD) is a highly prevalent process, characterized by lung involvement and by the presence of numerous systemic manifestations and/or extrapulmonary comorbidities.[1] These include nutritional disturbances and skeletal muscle dysfunction,[2,3] which are in turn interelated and determine per se worse prognosis.[4,5] Dysfunction of the respiratory muscles leads to difficulties in ventilation, especially when requirements are increased. Meanwhile, limb muscle dysfunction impairs both exercise capacity and numerous daily-life activities.[6] Although some causal factors are common to the various muscle groups of the body, others are more specific.[3] This is the case of changes in ventilatory mechanics that mainly affect the respiratory muscles, and the loss of condition derived from less physical activity, that mainly affects the lower-limb muscles.[3] In addition, the cellular and molecular mechanisms that contribute to dysfunction and associated structural and metabolic findings can be either general or specific to a muscle group.[7] Other consequences of the above factors and mechanisms include changes in muscle bioenergetics, which becomes less efficient, at least in the case of lower-limb muscles.[8] However, metabolic studies are associated with a number of important problems. On the one hand, in vivo studies require aggressive instrumentalization of the patient (e.g. catheterization of vessels entering and leaving the muscle),[8] and is not always technically possible. On the other hand, in vitro studies require the immediately processing of biopsy samples.[9] Therefore, few studies have evaluated the metabolic changes occurring in muscles with difficult access, such as breathing muscles, and most of these are performed using invasive procedures such as biopsy.[10–12] However, greater understanding of the use of energy substrates in the muscles of COPD patients may be useful in the management of muscle dysfunction and changes in body composition and nutritional status often associated with the disease.

Imaging techniques have advanced dramatically in recent years. One such technique, positron emission tomography (PET), provides guidance on the origin of various injuries based on the rate of uptake and utilization of key metabolites. This technique was used in 2005 to assess the activity of thoracic and abdominal muscles of COPD patients, and more qualitative activity was observed among healthy subjects.[13] A few years later, Osman et al. (2011) confirmed these findings by combining PET with computed tomography (CT) in inspiratory muscles.[14] We hypothesized that this combined technique might be useful for in vivo assessment with low invasiveness of simultaneous metabolic activity of respiratory and peripheral muscles, since structural and metabolic findings in biopsies of COPD patients are largely divergent.[3,7] Current radiotracer uptake measurement techniques will also allow more accurate observations. The aim of this study, therefore, was to obtain a general but quantitative evaluation of the synchronous metabolic activity of various muscle groups in COPD patients compared with that of patients with normal lung function.

Methods

Population

Candidates were initially all consecutive patients treated for pulmonary lesions, initially considered localized, in the Functional Unit of Lung Cancer in our institution (n=104). All subjects were scheduled for CT and PET for final disease staging. The study period was 10 months. Exclusion criteria were prior history of neoplastic disease, and other respiratory or inflammatory diseases. Patients suffering from other diseases that could cause false positives on PET, and those whose lung function tests did not strictly conform to normal or those with obstructive ventilatory impairment were also excluded. Patients in whom PET revealed extension of disease were also excluded. Sixty subjects were finally included, of whom 39 had a clinical history and pulmonary function tests consistent with the COPD.[1] The rest had no respiratory history and their forced spirometry and CO diffusing capacity values were within normal limits.

Design and Ethics

This is a retrospective cross-sectional study designed in accordance with local, national and international standards of human research (including the Code of Good Scientific Practice of our institution and the Declaration of Helsinki) and the Spanish Personal Data Protection Act (Act 15/1999 of 13th December on the Protection of Personal Data [*LOPD*]), and approved by the institution's Ethics Committee. All subjects gave written consent to use their medical information after being informed about the objectives and possible consequences of the study.

Techniques

Symptomatology, Anthropometrics and Lung Function

Personal data, symptomatology and various clinical aspects, together with anthropometric measurements (weight, height, and body mass index) were collected from each patient. Respiratory function was then tested, including spirometry with bronchodilator (Datospir 92, SIBEL, Barcelona, Spain), static lung volume and airway strength was tested using body plethysmography (Masterlab, Jaeger, Würzburg, Germany), carbon monoxide diffusing capacity was determined using the inbuilt gas meter of the same equipment ("one breath" technique), and arterial blood gas (Rapidlab 860 gas analyzer, Bayer, Chiron Diagnostics, GmbH, Tuttlingen, Germany). SEPAR recommendations were followed in all cases, except in gases, for which the published reference values for the local population were used.[15–17]