

The effects of a respiratory rehabilitation programme on body composition

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Abstract

English:

Objective: Analysis of the respiratory rehabilitation effects on body composition, performed for 10 patients with respiratory pathology.

Materials and method: In our pilot study were included patients with respiratory disease, for which bioelectrical impedance analysis was performed before and after an outpatient respiratory rehabilitation (RR) programme. The RR programme consisted of 20 sessions of exercise for lower limb (cycling and walking on a treadmill) and upper limb (weights).

Results: Ten patients followed the rehabilitation programme (five patients with chronic obstructive pulmonary disease, two with bronchiectasis, one with cystic fibrosis, one with lung cancer and one with idiopathic pulmonary fibrosis). Following the rehabilitation, they presented an important decrease in total body fat distribution (average total body fat distribution before RR – 31.38% and after RR – 27.09%, $p = 0.000$) and also segmental body fat distribution; we found an increase of total muscle mass after RR programme (average total muscle mass distribution before RR – 53.03 kg and after the RR – 56.84 kg, $p = 0.000$) and segmental muscle mass. The average body weight of the patients measured before and after the rehabilitation programme remained relatively constant in absolute value (81.8 kg and 81.3 kg after RR), probably by decreasing fat mass and increasing muscle mass. The RR programme had also a positive effect on increasing exercise tolerance (with 88.5 m at 6-min walk test) and dyspnoea improvement (decrease of mMRC scale with 1.5 points).

Conclusion: The RR programme has modified the body composition by increasing muscle mass and decreasing fat mass in the respiratory patients, with positive effects on symptoms and exercise tolerance.

Keywords

respiratory rehabilitation • impedantmetry • body composition

Efectele unui program de reabilitare respiratorie asupra compoziției corporale

Rezumat

Romanian:

Obiectiv: analiza efectelor unui program de reabilitare respiratorie (RR) asupra compoziției corporale, la 10 pacienți cu patologie respiratorie.


Material și metodă: În studiul nostru pilot am înrolat 10 pacienți cu patologie respiratorie, pentru care am efectuat cântărire cu impedanțmetrie înainte și după un program de reabilitare respiratorie multidisciplinar, de tip ambulator. Programul a fost alcătuit din 20 de ședințe compuse din antrenament pentru membrele inferioare (pedalare pe bicicleta ergometrică și mers pe covor rulant) și pentru membrele superioare (greutăți).

Rezultate: 10 pacienți au urmat programul de reabilitare respiratorie (cinci cu BPOC, doi cu bronșiectazii, unul cu fibroză chistică, unul cu neoplasm bronhopulmonar și unul cu fibroză pulmonară idiopatică). În urma programului, aceștia au prezentat o scădere importantă a masei grase totale (masă grasă totală medie înainte de programul de RR – 31.38%, după RR – 27.09%, $p = 0.000$), dar și corespunzătoare fiecărui segment corporal, precum și creșterea masei musculare totale (masă musculară totală medie

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înainte de RR 53.03 kg, după RR 56.84 kg, $p = 0.000$) și segmentare. Greutatea corporală medie a pacienților măsurată înainte și după programul de reabilitare respiratorie s-a menținut relativ constantă în valoare absolută (81.8 kg înainte și 81.3 kg după RR) probabil prin scăderea masei grase și prin creșterea masei musculare. Programul de RR a avut de asemenea un efect pozitiv asupra creșterii toleranței la efort (cu 88.5 m la testul de mers 6 min, $p < 0.05$) și asupra ameliorării dispneei (scăderea scorului de dispnee mMRC cu 1.5 puncte, $p < 0.05$).

Concluzie: programul de RR a dus la modificarea compoziției corporale în sensul creșterii masei musculare și scăderii masei grase la pacienții respiratori, cu efect pozitiv asupra simptomelor și toleranței la efort.

Cuvinte-cheie

reabilitare respiratorie • impedanțmetrie • compoziție corporală

Introduction

Respiratory rehabilitation (RR) is a non-pharmacologic therapy recommended by international guidelines for the treatment of symptomatic chronic obstructive pulmonary disease (COPD) and other respiratory patients. Dyspnoea represents the main factor leading to physical inactivity in respiratory patients, which further causes muscular weakness (peripheral and respiratory muscles) and limited exercise tolerance.

The rehabilitation programmes include physical training, respiratory physiotherapy, patient education, nutritional advice, psychological and tobacco cessation counselling. The rehabilitation's benefits are symptoms decrease, a better effort tolerance, decreased frequency of exacerbations and hospitalisation time and overall improvement of quality of life. Thus, the patient is allowed to be socially reintegrated (1–3). We conducted a small interventional prospective study on patients with various pulmonary pathologies in which we analysed RR effects on **body composition**. For patients with respiratory diseases, the modified nutritional status (either obesity or malnutrition/cachexia) can negatively influence the disease evolution.

COPD is a lung disease characterised by systemic inflammation with cardiovascular, metabolic, phosphorus-calcium balance and body composition consequences. In COPD patients, weight loss is a negative prognostic factor for morbidity and mortality (4–7). In these patients, for identical body mass index (BMI), either muscular mass (fat-free mass) or fat tissue could predominate (8).

Also in patients with **bronchiectasis**, the studies found a high percentage of fat-free mass depletion, independent of the aetiology of the disease and a systemic inflammation represented by high levels of inflammatory cytokines (9,10). Regarding **interstitial lung disease**, what is known so far is similar to COPD, although we need further studies. These patients have a lower muscle mass and a lower total body fat, many ILD subtypes being characterised by systemic inflammation, oxidative stress, hypoxaemia, impaired energy balance, malnutrition and accelerated biological ageing (11–13).

In **lung cancers**, cachexia is a common condition, especially in advanced stages. Weight loss is achieved by decreasing muscle mass. The mechanism is complex, involving systemic inflammation, cachexia, treatment side effects (14,15). In these patients, exercise programmes lead to increased muscle mass by enhancing protein synthesis and mitochondrial function.

Our study hypothesised that RR could lead to an improvement of the metabolic status and muscular wasting induced by the lack of physical activity, changes in body composition and systemic inflammation, common changes for all the pathologies suffered by the patients enrolled. Thus, changes in body composition may lead to symptoms, exercise tolerance and overall quality of life improvement for other chronic respiratory diseases also, not just for COPD.

Materials and method

This study was a pilot study and included the first 10 patients participating in our RR programme from Marius Nasta Institute of Pneumophysiology, Bucharest, in which body composition by bioimpedance was assessed. It was an outpatient programme, lasting approximately 2 months (three sessions per week, one session lasting 1 h).

- The RR programme consisted of 20 sessions of exercise for lower limb [20 min of cycling (Figure 1) and 20–30 min walking on a treadmill (Figure 2)] and upper limb [weights for 10 min (Figures 3 and 4)] and training sessions for the respiratory muscles. **Cardiopulmonary exercise testing** was used to determinate exercise capacity (power W) and maximal oxygen uptake (VO₂) and to prescribe the structure of a training session. Physical effort intensity was prescribed individually, set at 60% of the maximal power obtained during the cardiopulmonary exercise test.



Figure 1. Cycling during RR.



Figure 2. Treadmill exercise during RR.

Inclusion criteria: patients diagnosed with a chronic respiratory disease by a pulmonologist, with stable disease (no exacerbation in the last 3 months), with symptoms and decrease exercise capacity despite a maximal drug therapy.

Exclusion criteria: uncontrolled ischaemic heart disease (unstable angina, recent myocardial infarction – in the last 6 weeks), severe heart failure, uncontrolled cardiac arrhythmias, uncontrolled arterial hypertension, acute



Figures 3 and 4. Upper limb exercises.

thromboembolic disease, recent stroke (ischaemic/haemorrhagic), uncontrolled psychiatric disorders, temporary orthopaedic pathology, dementia, uncontrolled diabetes, large aortic aneurysm (only aerobic training is allowed, not resistance), lack of motivation, lack of adherence and failure to sign informed consent.

Informed consent was obtained from all the patients included in the study.

Parameters analysed before and after rehabilitation programme: dyspnoea, exercise capacity, anthropometric indices (BMI) and body composition:

- **mMRC (modified Medical Research Council) dyspnoea scale:** it is used to establish functional impairment due to dyspnoea in respiratory disease. It has five levels of severity (from 0 to 4, 4 being the worse dyspnoea level). The global initiative for obstructive lung disease (GOLD) treatment guidelines included the mMRC dyspnoea scale as a component of COPD patient's evaluation (3).
- **6MWT (six-min walking test):** this exercise test is used to assess aerobic capacity and endurance. The distance covered over a time of 6 min is used to compare changes in performance capacity. This is a test easy to perform, which needs a stopwatch, two cones, pulse-oximeter, Borg Dyspnoea Scale and a 30–50 m corridor (16). The test was performed in the early morning, two tests were performed and the highest distance value was noted.
- **Analysis of the body composition** (fat mass/dry weight analysis) was performed by using the InnerScanV-Segmental body composition monitor, Tanita BC-601- type bioanalysis (Figure 5). This device used the bioelectrical impedance analysis method to measure body composition with scientifically proven accuracy by sending low and safe electrical signals through the body. The parameters measured were: BMI, fat-free mass, percent of body fat, visceral fat area, skeletal muscle mass, segmental fat mass and segmental muscle mass (right arm, left arm, trunk, right leg left leg expressed as a percentage of normal or as kilograms), body water and bones mass.



Figure 5. Body composition monitor, Tanita BC-601.

Statistical data analysis

SPSS version 26 was used for statistical data analysis. The results were expressed as mean values \pm standard deviation or as median with minimum-maximum range. For the correlations between the variables with abnormal distribution, the Spearman correlation was used, and for the ones with the normal distribution, the Pearson correlation was used, the results being considered statistically significant for a value of $p < 0.05$.

For the comparison of variables with normal distribution (parametric) the Student's t -test was used and the statistically significant difference was considered at a value of $p < 0.05$.

Results

The **body composition** analysis was performed for 10 patients: five patients with COPD [stage II GOLD (one patient); stage III (one patient) and stage IV GOLD (three patients)], two patients with bronchiectasis, one patient with idiopathic pulmonary fibrosis, one patient with lung cancer and one patient with cystic fibrosis.

The rehabilitation programme was followed by 6 men and 4 women. Patients' age was between 34 and 77 years, with the mean age of 63.8 years.

Regarding BMI, the lower value was 20.15 kg/m² and the higher value was 35.1 kg/m², with the mean value 28.67 kg/m². Two patients were of normal weight, four patients were overweight and four patients were obesity.

More than half of the patients were active smokers or ex-smokers, as follows: three non-smokers, two active smokers and five ex-smokers.

The 6-min walk test (6MWT) was performed for all patients before and after RR. We observed an increase in average distance with 88.5 m (6MWT average distance before RR: 340.5 m; 6MWT average distance after RR: 429 m), $p = 0.000$ ($p < 0.05$, student's t -test).

The degree of dyspnoea was analysed before and after RR, using the mMRC scale. After the RR programme, we noticed a significant improvement of the dyspnoea, as the mMRC score decreased with 1.5 points (before RR: mMRC average score- 3.1 points; after RR: mMRC average score 1.6 points), $p = 0.000$ ($p < 0.05$, student's t -test).

Changes in the body composition of the patients who have performed RR programme

1. After the RR programme, the average weight of the patients was 81.3 kg, compared with 81.8 kg before RR, with 0.5 kg lower, which was statistically significant, $p = 0.000$ ($p < 0.05$, student's t -test).
2. The percentage of average total body fat changed statistically significant after the rehabilitation programme, from 31.83 to 27.09%, $p = 0.000$ ($p < 0.05$, student's t -test).
3. Following exercises performed during the RR programme, we observed that fat distribution on body segments (%) was decreased in the upper, lower limbs and trunk (Figure 6). The decrease was statistically significant:
 - right arm from 26.29 to 23.33% ($p = 0.008$, student's t -test)
 - left arm from 26.9 to 22.9% ($p = 0.025$, student's t -test)
 - right leg from 30.1 to 25.81% ($p = 0.004$, student's t -test)
 - left leg from 30.1 to 25.75% ($p = 0.003$, student's t -test)
 - trunk from 33.22 to 27.32% ($p = 0.025$, student's t -test).
4. The total muscle mass distribution (kg) was statistically significantly higher after the rehabilitation programme, from 53.03 kg (average total muscle mass before RR) to 56.84 kg (average total muscle mass after RR), $p = 0.000$ ($p < 0.05$, student's t -test).
5. The average muscle mass distribution on body segments (kg) after the RR programmes was higher for arms and legs but is almost unchanged for the trunk. For the right arm: from 2.9 to 3.43 kg, for left arm: from 3.1 to 3.3 kg, for right leg: from 8.7 to 9.3 kg, for left leg: from 8.6 to 9.32 kg and for the trunk: from 31.6 to 3.3 kg (Figure 7).

The distance performed at 6MWT was positively correlated with total fat mass measured before RR programme

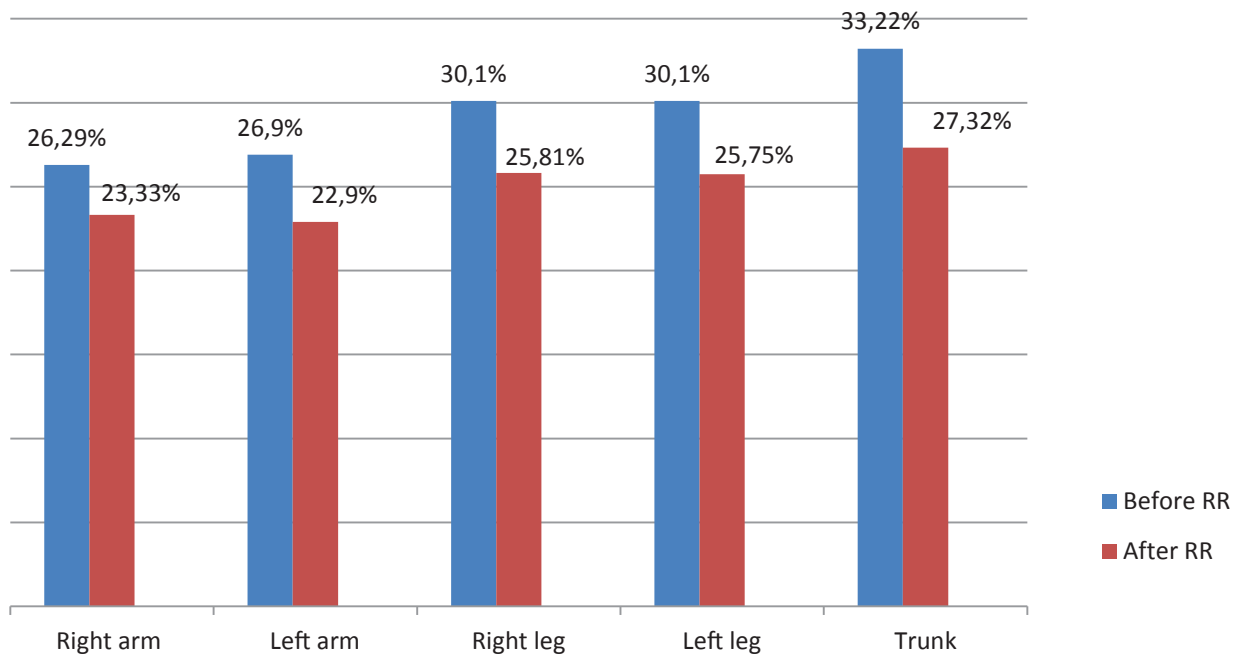


Figure 6. Changes on average body fat distribution on body segments (%), before and after RR ($p < 0.05$, statistically significant).

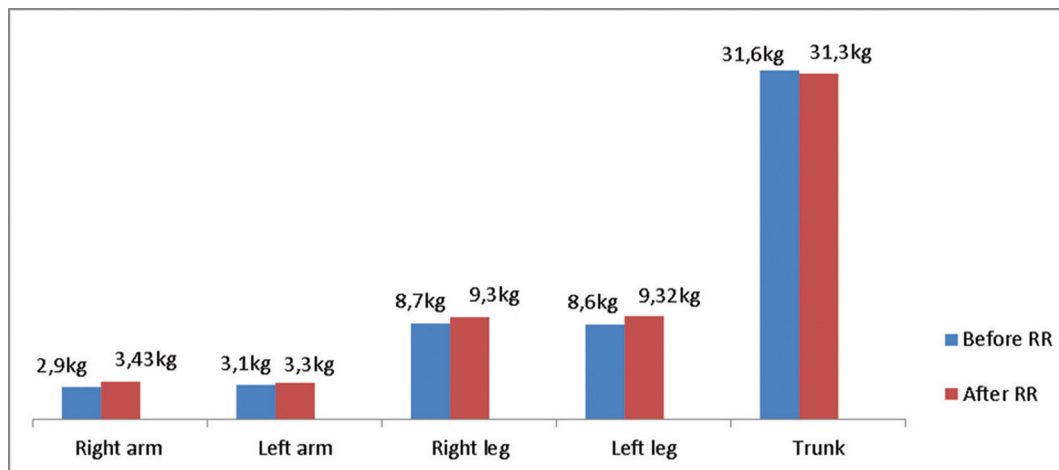


Figure 7. Average muscle mass distribution on body segments (kg), before and after RR.

($r = 0.253$, $p = 0.138$) (Figure 8), and we have a stronger positive correlation after the RR programme ($r = 0.422$, $p = 0.042$) (Figure 9).

These results may suggest that the improvement of effort tolerance in respiratory patients after the RR programme is influenced also by the decrease in fat mass, not only by increase in muscle mass.

We did not find significant correlations between total muscle mass and severity of dyspnoea measured by mMRC scale before RR ($r = 0.364$, $p = 0.3$; $r =$ Pearson correlation index;

statistically significant for $p < 0.05$) and after RR ($r = 0.115$, $p = 0.75$; $r =$ Pearson correlation index; statistically significant for $p < 0.05$).

Discussion

The majority of the literature data analysed changes in body composition in COPD patients, and have shown that losing weight and muscle mass is a negative prognostic

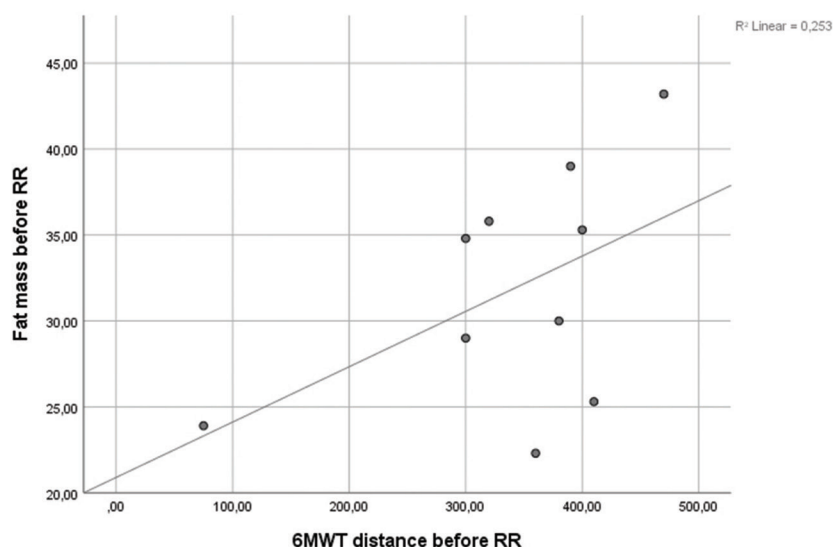


Figure 8. Correlation between the 6MWT distance and the total fat mass before RR programme ($r = 0.253$, $p = 0.138$); r = Pearson correlation index; statistically significant for $p < 0.05$.

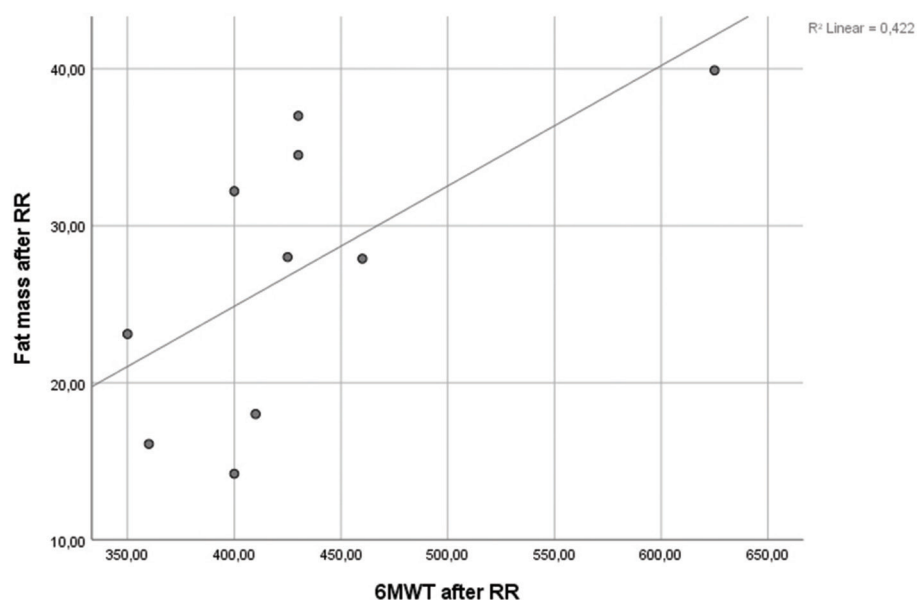


Figure 9. Correlation between the 6MWT distance and the total fat mass after RR programme ($r = 0.422$, $p = 0.042$); r = Pearson correlation index; statistically significant for $p < 0.05$.

factor (4–7,17). Our study intended to analyse the body composition changes before and after rehabilitation in various pulmonary pathologies: COPD in different stages of severity but also bronchiectasis, idiopathic pulmonary fibrosis, lung cancer and cystic fibrosis.

We chose to include in our study patients with different respiratory diseases, even if we present a small number of

patients, because previous studies have shown that most of the chronic respiratory diseases have relatively similar changes: weight loss is achieved by decreasing muscle mass and systemic inflammation (8,9–15).

All of our patients had a BMI > 18 kg/mp (more than half of the patients were overweight or obese). From the experience of our rehabilitation centre, patients with more severe

pathology and low BMI have a lower degree of adherence to an outpatient RR programmes, and for this one, it may be recommended an inpatient rehabilitation programme. The low BMI (by decreased skeletal muscle mass), especially in COPD patients, is a characteristic of severe disease, with a higher mortality rate (4–7).

The determination of body composition was performed with a specialised bioanalysis device (useful to determine the fat and dry mass percent, body water, total and per body segments). The results obtained by this device are more capable to detect the finest changes in body composition, compared with the usual commercial weight scales.

Regarding the results obtained, our 2 months outpatient RR programme led to statistically significant changes in the body composition of our respiratory patients. Although the average body weight did not decrease significantly, we observe an increase in muscle mass and a decrease in body fat mass. For patients with the same BMI can predominate fat or muscle mass, which can explain different effort tolerance and symptomatology in patients with the same weight.

The body composition changes had a positive effect on increasing exercise tolerance (assessed by the 6MWT) and improvement of dyspnoea (assessed by the mMRC scale). The results are similar to the other studies (18–20), which conclude that fat-free mass, independently of airflow obstruction, is an important determinant of exercise performance in patients with severe COPD and improvements in exercise performance and muscle function are proportionally larger than increases in fat-free mass.

Previous studies showed that 6MWT distance improves according to an increase in total muscle mass (18–20). In the current analysis, the RR led to an exercise tolerance improvement with 88.5 m at 6MWT and a decrease of the fat mass from 31.83 to 27.09%. The distance performed at 6MWT was positively correlated with total fat mass measured before RR programme ($r = 0.253$, $p = 0.138$), and we have a stronger positive correlation for these two parameters after the RR programme ($r = 0.422$, $p = 0.042$).

These results make us conclude that the improvement of effort tolerance in respiratory patients after the RR programme is influenced not only by the increase in total fat-free mass but also by the decrease in fat mass.

In the case of our study patients, the rehabilitation leads also to symptoms improvement, with the decrease of average mMRC dyspnoea score from 3.1 points to 1.6 points, which was statistically significant ($p < 0.05$).

The relation between body weight, symptoms and exercise tolerance represents the basis of BODE index. The components of this index are: BMI, 6-min walk distance, mMRC dyspnoea scale and forced expiratory volume in the first second. Studies in COPD patients have shown that BODE index is a survival predictor, better than FEV1

(21), and patients with higher BODE scores were at higher risk for a fatal disease evolution. The study performed by Cotte showed that in 116 COPD patients that followed a rehabilitation programme, there was an improvement of BODE index, with better outcomes (22).

Another study demonstrates that there is a relationship between body composition and mortality. It included 412 patients with moderate-severe COPD, and the results showed that the fat-free mass index was an independent predictor of survival, but the fat mass index was not. Forty-five per cent of patients with cachexia died at 5 years of follow-up visit (23).

The benefits for COPD patients after the changes in body composition were also demonstrated by the Cochrane review conducted by Ferreira, in which the results of 17 studies with 632 participants who received nutritional support were analysed. The conclusion was that, especially in the malnourished COPD patients, nutritional supplementation can lead to changes in body composition by increasing muscle mass, reversing weight loss, with better exercise tolerance and overall improvement of quality of life (24). Therefore, it may be possible that by adding a diet to a pulmonary rehabilitation programme to obtain more important changes in body composition.

The limits of the study were the small number of patients, especially for other pathologies than COPD and the absence of a category of patients underweight.

However, it was a small pilot study and as research idea for the future it is to analyse a large number of patients, to find correlations between body composition and other parameters used to define COPD severity/prognosis and also for other respiratory pathology to see if the body composition changes increase the survival in chronic respiratory diseases.

Conclusion

This study shows changes after RR in body composition for patients with different respiratory pathologies, with a decrease in fat mass and also an increase in muscle mass. The body composition changes had a positive effect on exercise tolerance and dyspnoea. The analysis of total and segmental body composition may be a useful tool in RR programmes to establish an individualised programme of exercises and to obtain an improvement of the patients' life.

Ethical approval

Inform consent was obtained from the patients in order to participate to the study and write the article.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *American Journal of Respiratory and Critical Care Medicine*. 2006;173: 1390–1413.
2. Tudorache VM, Lovin S, Friesen M. *Tratat de reabilitare pulmonară*. Ed Mirton, Timisoara; 2009.
3. *Global Strategy for the Diagnosis, Management and Prevention of COPD*, Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report; 2019. Available from: <http://www.goldcopd.org>.
4. Sabino PG, Silva BM, Brunetto AF. Nutritional status is related to fat-free mass, exercise capacity and inspiratory strength in severe chronic obstructive pulmonary disease patients. *Clinics (Sao Paulo)*. 2010;65(6): 599–605.
5. Vestbo J, Prescott E, Almdal T, Dahl M, Nordestgaard BG, Andersen T, et al. Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. *American Journal of Respiratory and Critical Care Medicine*. 2006;173: 79–83.
6. Vermeeren MAP, Creutzberg EC, Schols AMWJ, Postma DS, Pieters WR, Roldaan AC, et al. Prevalence of nutritional depletion in a large out-patient population of patients with COPD. *Respir Med*. 2006;100: 1349–1355.
7. Cao C, Wang R, Wang J, Bunjhoo H, Xu Y, Xiong W. Body mass index and mortality in chronic obstructive pulmonary disease: a meta-analysis. *PLoS One*. 2012;7(8): e43892. doi: 10.1371/journal.pone.0043892.
8. Eid AA, Ionescu AA, Nixon LS, Lewis-Jenkins V, Matthews SB, Griffiths TL, et al. Inflammatory response and body composition in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*. 2001;164: 1414–1418.
9. Oliveira G, Oliveira C, Gaspar I, Porras N, Martín-Núñez G, Rubio E, et al. Fat-free mass depletion and inflammation in patients with bronchiectasis. *Journal of the Academy of Nutrition and Dietetics*. 2012;112(12): 1999–2006.
10. Martínez-García MA, Perpiña-Tordera M, Román-Sánchez P, Soler-Cataluña JJ, Carratalá A, Yago M, et al. The association between bronchiectasis, systemic inflammation, and tumor necrosis factor alpha. *Archivos de bronconeumología*. 2008;44: 8–14.
11. Alakhras M, Decker PA, Nadrous HF, Collazo-Clavell M, Ryu JH. Body mass index and mortality in patients with idiopathic pulmonary fibrosis. *Chest*. 2007;131(5): 1448–1453.
12. Rahman I, Skwarska E, Henry M, et al. Systemic and pulmonary oxidative stress in idiopathic pulmonary fibrosis. *Free Radical Biology & Medicine*. 1999;27(1–2): 60–68.
13. Snetelaar R, van Moorsel CH, Kazemier KM, van der Vis JJ, Zanen P, van Oosterhout MF, Grutters JC. Telomere length in interstitial lung diseases. *Chest*. 2015;148(4): 1011–1018.
14. Argiles JM, Busquets S, Stemmler B, Lopez-Soriano FJ. Cancer cachexia: understanding the molecular basis. *Nature Reviews Cancer*. 2014;14: 754–762.
15. Al-Majid S, Waters H. The biological mechanisms of cancer-related skeletal muscle wasting: the role of progressive resistance exercise. *Biological Research for Nursing*. 2008;10: 7–20.
16. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *American Journal of Respiratory and Critical Care Medicine*. 2002;166(1): 111–117.
17. Gologanu D, Ionita D, Gartonea T, Stanescu C, Bogdan M.A. Body composition in patients with chronic obstructive pulmonary disease. *Maedica (Buchar)*. 2014;9(1): 25–32.
18. Schols AM, Mostert R, Soeters PB, Wouters EF. Body composition and exercise performance in patients with chronic obstructive pulmonary disease. *Thorax*. 1991;46: 695–699.
19. Franssen FM, Broekhuizen R, Janssen PP, Wouters E, Schols A. Effects of whole-body exercise training on body composition and functional capacity in normal-weight patients with COPD. *Chest*. 2004;125: 2021–2028.
20. Abbatecola AM, Fumagalli A, Spazzafumo L, Betti V, Misuraca C, Corsonello A, et al. Body composition markers in older persons with COPD. *Age Ageing*. 2014;43(4): 548–553.
21. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *The New England Journal of Medicine*. 2004;350(10): 1005–1012.
22. Cote C.G, Celli BR. Pulmonary rehabilitation and the BODE index in COPD. *The European Respiratory Journal*. 2005;26: 630–636.
23. Schols AM, Broekhuizen R, Weling-Scheepers CA, Wouters EF. Body composition and mortality in chronic obstructive pulmonary disease. *The American Journal of Clinical Nutrition*. 2005;82(1): 53–59.
24. Ferreira IM, Brooks D, White J, Goldstein R. Nutritional supplementation for stable chronic obstructive pulmonary disease. *The Cochrane Database of Systematic Reviews*. 2012;12: CD000998.