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Pulmonary Rehabilitation in Multimorbidity and Multiple Disabilities

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In Chronic Obstructive Pulmonary Disease (COPD) patients, it has been proven that Pulmonary Rehabilitation (PR) helps in increasing the exercise ability, in easing the difficulty in breathing, in improving Health Related – Quality of Life (HR-QoL) and in decreasing the period in hospital and the utilization of medical resources.1

Although there is insufficient evidence to determine whether PR improves survival in patients with COPD, this lack of evidence does not necessarily indicate that PR has no effect on survival, but in order to be reasonably powered to detect an effect of this magnitude the sample size would have to be a magnitude larger than those found in existing studies.2 Moreover, PR program significantly showed a large decrease in the risk of death in rehabilitated patients as measured using the BODE index.3 The timed walk distance and MRC-rated dyspnea do improve with PR, and these variables are correlated with survival in patients with COPD.2

In contrast, Cardiac Rehabilitation (CR) improves prognosis (reduce all-cause mortality and cardiac death), exercise capacity, QoL of patients by reducing symptoms associated with Activities of Daily Living (ADL) in patients with ischemic heart failure and Coronary Artery Disease (CAD).4

Moreover, Renal Rehabilitation (RR) including exercise training in patients with hemodialysis improves in VO2 max, left ventricular function, cardiac sympathetic and parasympathetic disharmony, malnutrition-inflammation-atherosclerosis syndrome, anemia, sleep quality, anxiety, HR-QoL, activities of daily living, shunt size, Kt/V and mortality.5

Until a recent date, medicine has aimed to prolong the life expectancy; that is, “Adding Years to Life” (improvement of vital prognosis) has been the focus of the medicine. In addition, the extension of disability-free life expectancy has become the major target of medicine by trying to prevent the diseases that may cause disabilities.

The rehabilitation medicine has been proactively implemented to accomplish the concept of “Adding Life to Years (the improvement of living functions and QoL)” by helping overcome the disabled conditions through the assessment of and intervention in socially disadvantaged functions.6 In recent, it was found that the rehabilitations of internal organ impairment such as CR and RR have been useful to accomplish the concept of not only “Adding Life to Years” but also “Adding Years to Life” (“Adding Life to Years and Years to Life”).6

COPD often coexists with other diseases (comorbidities such as ischemic heart disease, chronic kidney disease, osteoporosis) that may have a significant impact on prognosis. Thirty-three percent of elderly patients with heart failure had COPD and 25% of elderly patients with COPD also had heart failure.7 This risk of comorbid disease can be increased by the sequelae of COPD, e.g., reduced physical activity. As super-aged society has come, the number of persons with Multimorbidity and Multiple Disabilities (MMD)8 and their needs of rehabilitation have
increased rapidly more than we have expected. In CR or RR in patients with COPD, CR should be done according to usual CR guidelines as there is no evidence that CR or RR should be done differently in the presence of COPD.

Generally the rehabilitation is effective for people whose physical strength is deteriorated and it may be so for persons with MMD. Considering the results of the survey on disabilities and the report that the death rate of dialysis patients who experienced the cardiac infarction has decreased by 35% owing to the rehabilitation treatment.

In the era of MMD, the rehabilitation needs to consider the existing principle of FITT (Frequency, Intensity, Type, Time). The unique problems of each organ and the relationship among them such as brain, heart, lung and bone joints should be considered simultaneously. For example, even a simple walk may lay a burden on the patient’s heart, because the energy consumption during the walk of the patients with hemiplegic stroke remarkably increases of the energy consumption. Therefore, exercise therapy needs to be implemented with using walking stick in the early stage of rehabilitation, because the energy consumption during the walk may be reduced by using walking stick. In the case of the co-occurrence of stroke and chronic heart failure, the criteria of exercise therapy depends on the criteria of heart failure.

The more studies on the rehabilitation of persons with MMD need to be implemented, because the contents of rehabilitation including the exercise intensity and hours to accomplish “Adding Life to Years” may be different from those to do “Adding Life to Years and Years to Life”. As to the rehabilitation medicine in the era of MMD, it is important that individualized programs should be prepared considering the condition of entire body or risk factors of the patients, their social or environmental conditions comprehensively and, most of all, which to choose “Adding Life to Years” or “Adding Life to Years and Years to Life”.

REFERENCES


3. Cote CG, Celli BR. Pulmonary rehabilitation and the BODE index in COPD. Eur Respir J. 2005; 26: 630-636. doi: 10.1183/09031936.05


Pulmonary Aspergillosis Mimicking Primary Lung Cancer

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KEYWORDS: Pulmonary aspergillosis; Mimicking lung cancer; Thoracic CT.

A 68-year-old man was transferred to our hospital because of abnormal lung nodule. He was a social drinker and a current smoker with a history of 70 pack-years. He had no symptoms and was a good nutritional status. Based on the pulmonary function tests, he was diagnosed with chronic obstructive lung disease stage II by Global Initiative on Obstructive Lung Disease staging system. Thoracic Computed Tomography (CT) showed the irregular-shaped nodule measuring 15 mm in size with spiculation at right S1 (Figure A), which accompanied by emphysematous lung changes. On thoracic FDG PET/CT, the nodule demonstrated the intense standardized uptake values both in the early (max 3.4) and delayed (max 4.2) phases, suggesting malignancy (Figure B). However, video-assisted thoracic surgery biopsied specimens on Hematoxylin and eosin stains showed that the nodule was consisted of central necrotic component surrounded by microabscesses and fibrotic granulomatous tissues (Figure C) in which contained filamentous fungi on Grocott’s methenamine silver stain (Figure D) with calcium oxalate crystal deposition, indicating of pulmonary aspergillosis. Pulmonary aspergillosismimicking cancer was an extremely rare event, but should be included in the differential diagnosis for solitary pulmonary nodule.
CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

REFERENCES


Primary Pleural Lymphoma with Dense Pleural Thickening

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ABSTRACT

A 72-year-old man was referred to our hospital because of persistent right chest pain and an abnormal shadow on chest X-ray. Thoracic computed tomography showed a right upper pleural nodule and massive right pleural thickening with an ipsilateral pleural effusion, which partially extended to the left pleura. The pleural tumor showed an intense standardized uptake value of 28.5 on fluorodeoxyglucose positron emission tomography/computed tomography. After performing a thoracic pleural biopsy, a diagnosis of primary pleural lymphoma, diffuse large B cell type, was made. Primary tumors account for about 5-10% of pleural neoplasms, which of 2.4% accounts for primary pleural lymphoma. Although, primary pleural lymphoma is an extremely rare tumor, it should be considered in the differential diagnosis of pleural thickening in the costophrenic recess with pleural effusion even if the patient has no apparent history of pyothorax associated with Epstein-Barr virus infection.

KEYWORDS: Primary pleural lymphoma; Diffuse large B cell lymphoma; Pleural thickening; Thoracic computed tomography.

INTRODUCTION

Primary pleural lymphoma is an extremely rare disorder, accounting for 2.4% of primary chest wall tumors.1,2 The clinical manifestations and characteristic pleural thickening on thoracic computed tomography are clinical clues to the diagnosis. A case of primary pleural lymphoma, diffuse large B cell type, with thickened pleura and ipsilateral pleural effusion as the initial presentation, is reported.

CASE REPORT

A 72-year-old man was referred to our hospital because of a 1-month history of persistent right chest pain. He had been in good health except for normal pressure hydrocephalus two years previously. He worked as a landscape gardener and had no illicit drug or dust exposure, including asbestos. On initial examination, he appeared well, and vital signs and physical examination were normal. Chest X-ray showed a solitary nodule measuring 15 mm in size with an extrapleural sign in the right upper lung field, as well as blunting of the right costophrenic angle (Figure 1A). Thoracic Computed Tomography (CT) confirmed the bulging nodule at the right parietal pleura and a bulky right pleural mass with a pleural effusion (Figures 1B and 1C). Both thoracic CT (Figure 1C) and Fluorodeoxyglucose (FDG) Positron Emission Tomography/Computed Tomography (PET/CT) (Figure 2) showed that the right pleural mass partially extended...
to the left pleura and invaded to the spinal canal through the right intervertebral foramen, which showed an intense Standardized Uptake Value (SUV) of 28.5, suggesting malignancy. Serum laboratory examinations were normal except for mild anemia, mild elevation of Lactase Dehydrogenase (LDH) (230 IU/L), C-reactive protein (1.3 mg/dL), and soluble interleukin-2 receptor (956 U/mL). Furthermore, no elevation of serum tumor markers such as Carcinoembryonic antigen (CEA) (1.8 ng/mL, normal range <5.0 ng/mL), carbohydrate antigen 19-9 (5.7 U/mL, normal range <37.0 U/mL), squamous cell carcinoma antigen (1.4 ng/mL, normal range <1.5 mg/mL), and neuron-specific enolase (8.6 ng/mL, normal range <10.0 ng/mL) were noted. Thoracentesis demonstrated elevation of the total cell count (4,200 /μL; with lymphocytes 87%, neutrophils 6%, monocytes 6%), total proteins of 4.3 g/dL, and LDH of 200 IU/L, suggesting a chronic exudative pleural effusion. The values of CEA (0.8 ng/mL), adenosine aminohydrolase (25.1 IU/L), and hyaluronic acid (43,900 ng/mL) in the pleural fluid were normal, and the cytological assessment was class II.

On thoracoscopy, protrusion of the surface of the parietal pleura with white colored central necrosis together with dilatation of the capillary vessels at the normal site (Figure 3) was noted. On hematoxylin and eosin staining, the diagnostic thoracoscopic pleural biopsy specimens demonstrated abundant large atypical cells (Figure 4) that were immunohistochemically positive for CD20 (Figure 4, inset), CD79a, CD10, and Bcl2, but negative for cytokeratins and calretinin.

Based on these findings, he was diagnosed with primary pleural lymphoma, diffuse large B cell lymphoma (DLBCL), Ann Arbor stage II. Thereafter, he was treated with 6 consecutive courses of R-CHOP chemotherapy (R: rituximab (375 mg/m² on day 1), C: cyclophosphamide (750 mg/m² on day 2), H: doxorubicin hydrochloride (50 mg/m² on day 2), O: vincristine sulfate (1.4 mg/m² on day 2), and P: prednisone 100 mg/body on days 2 to 6), which resulted in complete remission, and he was discharged uneventfully.
and/or chest pain, as in the present case. Filly et al. pulmonary lymphoma are pleural effusion, pleural thickening, In general, clinical clues to the diagnosis of primary lymphoma (HL) and 10% of patients with Non-Hodgkin's Lymphoma (NHL) present with or subsequently develop pleural involvement during the course of disease, primary pleural lymphoma is an extremely rare disorder, accounting for 2.4% of primary chest wall tumors. The most frequent type of lymphoma involving the pleura is DLBCL, followed by follicular lymphoma, with rates of approximately 60% and 20%, respectively, as was the present case.

In general, clinical clues to the diagnosis of primary pulmonary lymphoma are pleural effusion, pleural thickening, and/or chest pain, as in the present case. Filly et al. reported that pleural effusion was seen in 7% of patients with Hodgkin’s lymphoma (HL) and 10% of patients with NHL who were previously untreated. The mechanisms of pleural effusion in primary pleural lymphoma can be due either to impaired lymphatic drainage because of mediastinal adenopathy or pleural or pulmonary infiltration, or to thoracic duct obstruction. The pleural effusion in NHL appears to be caused by impaired lymphatic drainage, and that of HL was due to direct pleural infiltration of tumor cells. The precise reason is unknown, but the mode of spread is rather lymphatic in HL, and contiguous and/or hematogenous in NHL, which may explain the higher affinity to parietal pleura in NHL. Similarly, though the reason is unknown, pleural involvement can be unilateral or bilateral and is more common on the left side.

Regarding radiological findings, primary pleural lymphoma can present as an enhancing mass in the costophrenic recess with pleural effusion, corresponding to pleural thickening and/or nodular pleural infiltration, which needs differentiation from primary pleural tumors including malignant mesothelioma or other metastatic pleural diseases, as in the present case.

The tumor development mechanisms of malignant lymphoma arising in the pleura have not yet been established, but Hirai et al. demonstrated that all of nine Japanese patients with primary pleural lymphoma without a history of pyothorax had no Epstein-Barr virus (EBV) infection, as in the present case (figure not shown).

This case showed unique clinical presentation of primary pleural lymphoma in that 1) massive right pleural thickening with an ipsilateral pleural effusion, 2) no history of pyothorax associated with EBV infection. Thus, this case reminds us of the fact that we should be aware of the possibility of primary pleural lymphoma as an extremely rare tumor if the patient has pleural thickening with pleural effusion, even with no history of chronic pyothorax.

REFERENCES


Hydrogen Sulfide in Airway Diseases

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Hydrogen Sulfide (H₂S) is a colorless, water-soluble gas with the odor of rotten eggs. H₂S can be produced via non-enzymatic pathways, but is mainly synthesized from L-cysteine as the substrate by Cystathionine-γ-lyase (CSE), Cystathionine-β-synthetase (CBS) and 3-mercaptopyruvate sulfur transferase (3MTS). H₂S is now recognized as the third signaling gasotransmitter after Carbon monoxide (CO) and Nitric Oxide (NO), and it plays an important role in the pathophysiology of airway disease, such as asthma and Chronic Obstructive Pulmonary Disease (COPD).

H₂S AND ASTHMA

Asthma is a chronic airway disorder characterized as airway inflammation, airway hyper responsiveness (AHR), and airway remodeling, which is caused by inflammatory cells such as eosinophils, mast cells, T-helper 2 (Th2) lymphocytes, neutrophils, and structural cells such as airway epithelial cells and airway smooth muscle cells (ASMCs). The levels of H₂S in serum were decreased in patients with stable asthma or acute exacerbation asthma. The changes in serum H₂S levels or exhaled air were positively correlated with FEV₁% and negatively with the total count of sputum cells and neutrophils percentage. Similar findings were observed in pediatric asthmatics. The serum levels of H₂S were significantly decreased in asthmatic children compared to healthy children and the levels were positively correlated with lung function. Therefore, it was proposed that H₂S level could be used as a biomarker for asthma.

Animal studies showed that the serum H₂S level, the production rate of H₂S in lung tissue, and the expression of CSE were decreased in an Ovalbumin (OVA)-induced rat model of asthma.

Exogenous supplementation with Sodium Hydrogen Sulfide (NaHS, an exogenous donor of H₂S) improved the airway flow and attenuated airway inflammation and remodeling in the model, while inhibition in the synthesis of H₂S aggravated the development of airway inflammation and AHR.

H₂S AND COPD

Chronic Obstructive Pulmonary Disease (COPD) is a chronic airway disease characterized by chronic inflammation and parenchymal destruction (emphysema), which ultimately contributes to irreversible airflow obstruction. Cigarette Smoke (CS) or other noxious particles are the main etiologic factors for the development of COPD. A clinical study investigating the relation of serum H₂S levels to the severity of COPD showed that serum H₂S levels were significantly higher in patients with stable COPD than in patients with Acute Exacerbation of COPD (AECOPD) and control subjects. Serum H₂S levels were positively correlated with the percentage of predicted FEV₁ value, and negatively correlated with the proportion of neutrophils in sputum in all patients. This study indicated that H₂S may be involved in the pathogenesis of airflow obstruction in COPD and may be connected with disease activity and severity. Moreover, sputum H₂S levels were higher in AECOPD patients than those in stable COPD patients. Thus, the high sputum-to-serum ratio of H₂S may indicate an ongoing neutrophilic inflammation.
The important role of H\textsubscript{2}S in COPD was further confirmed through animal studies. Han, et al. showed that chronic CS could down-regulate the expression of CSE and CBS in the rat lung, while treatment with NaHS could inhibit both airway inflammation and airway remodeling as well as attenuate the development of emphysema and pulmonary artery hypertension.\textsuperscript{10} Another study showed that the treatment with NaHS reduced the airway inflammation and AHR caused by Cigarette Smoke (CS) while treatment with PPG (the inhibitor of CSE) further aggravated the development of airway inflammation and AHR due to the inhibition of the production of endogenous H\textsubscript{2}S.\textsuperscript{11}

THE ROLE OF H\textsubscript{2}S IN MODULATING AIRWAY DISEASE

Anti-inflammatory

Presently, most studies demonstrate that H\textsubscript{2}S possesses an anti-inflammatory function in many models of respiratory disease, including asthma.\textsuperscript{6,7} COPD.\textsuperscript{10,11} Although the anti-inflammatory mechanism of H\textsubscript{2}S is not clear, the exogenous addition of H\textsubscript{2}S could inhibit Th2-cytokines like IL-5 and IL-13 in addition to eotaxin-1 in the BAL fluid in an OVA-induced murine asthma model.\textsuperscript{7} Treatment with NaHS could decrease the production of pro-inflammatory cytokines such as IL-6 and IL-8 and increase the production of anti-inflammatory cytokines such as IL-10 in the plasma and lung tissues.\textsuperscript{12}

Anti-oxidative

H\textsubscript{2}S can freely cross the plasma membrane and the mitochondrial membrane to scavenge Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS).\textsuperscript{13} Moreover, H\textsubscript{2}S enhances the production of reduced Glutathione (GSH) by enhancing cystine/cysteine transporters and redistributes GSH to mitochondria.\textsuperscript{14} NaHS increased the ratio of reduced/oxidized glutathione (GSH/GSSG) and decreased the content of 8-hydroxy-deoxyguanosine (8-OHdG) in the lungs of CS-exposed mice,\textsuperscript{10} which was similar to our findings that NaHS inhibited ozone-induced oxidative stress in a murine model.\textsuperscript{15} Benetti, et al. confirmed that NaHS treatment abolished the increased lipid peroxidation in the allergic mouse lungs and increased Superoxide dismutase (SOD), Glutathione peroxidase (GPx) and Glutathione Reductase (GR) enzyme activities.\textsuperscript{16} Nuclear factor (erythroid-derived 2)-like 2, also known as Nrf2, is a key transcription factor that regulates the expression of many important antioxidant proteins that protect against oxidative damage triggered by injury and inflammation.

Regulation of Cell Proliferation and Apoptosis

H\textsubscript{2}S can inhibit cell proliferation; however, the effects of H\textsubscript{2}S on cellular apoptosis are complex. An in vitro study showed that both NaHS (the fast-releasing H\textsubscript{2}S donor) and GYY4137 (the slow-releasing H\textsubscript{2}S donor) suppressed human Airway Smooth Muscle Cell (ASMC) proliferation induced by Fetal Bovine Serum (FBS) and the proinflammatory cytokines IL-1\textbeta\textsuperscript{1} and IL-8.\textsuperscript{17} H\textsubscript{2}S decreased the migration and proliferation of a human lung fibroblast cell line (MRC5) stimulated by FBS and basic Fibroblast Growth Factor (bFGF), which is probably related to the fact that H\textsubscript{2}S inhibits ERK-1/2 phosphorylation in MRC5 cells.\textsuperscript{18}

Inhibitory Effect on AHR

Animal experiments showed that NaHS reduced the AHR caused by OVA,\textsuperscript{7} ozone,\textsuperscript{19} and cigarette smoke,\textsuperscript{21} while treatment with PPG aggravated the development of AHR. The underlying mechanism may be related to the direct relaxant effect on bronchial smooth muscle as well as anti-inflammatory and anti-oxidative effects of NaHS. Kube, et al. found that NaHS relaxed the carbachol-precontracted mouse bronchial rings, and this relaxant effect was not affected.\textsuperscript{20} The mechanism may be due to that NaHS activates large conductance Calcium activated potassium channels (BKCa) or activates K (ATP) channels in airway smooth muscle cells.\textsuperscript{21,22}

Inhibitory Effect on Airway Remodeling

NaHS inhibited goblet cell hyperplasia, airway mucus secretion, collagen deposition, and subepithelial fibrosis in an OVA-induced rat asthma model.\textsuperscript{4} NaHS also inhibited increases in bronchial thickness in a CS-induced mouse emphysema model.\textsuperscript{10} NaHS reduces increases in right ventricular systolic pressure, the thickness of pulmonary vascular walls, and the ratio of right ventricle/left ventricle+septum in a CS-induced mouse emphysema model.\textsuperscript{10} The inhibitory effect on vascular remodeling by H\textsubscript{2}S may be related to the roles of H\textsubscript{2}S in promoting the apoptosis of pulmonary artery SMC,\textsuperscript{18} and in reducing collagen deposition in the pulmonary vasculature.\textsuperscript{23}

PERSPECTIVE

H\textsubscript{2}S is a novel gas molecule with many biological effects. More research is needed to clarify the metabolism and mechanism of H\textsubscript{2}S in airway diseases. Clinical studies have shown that the level of H\textsubscript{2}S in plasma, sputum, and exhaled breath could reflect the disease condition and severity of asthma or COPD. Since H\textsubscript{2}S plays many roles in airway disease, more focused studies about the effects of H\textsubscript{2}S on respiratory protection is urgently needed. Currently, some pharmaceutical companies are developing slow-releasing, controllable H\textsubscript{2}S donors and H\textsubscript{2}S-releasing hybrid drugs. These drugs may pave new way for the treatment of airway diseases.

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REFERENCES


Effects of the Resisted Exercise in the Respiratory Function of Individuals with Hemiparesis after Stroke

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ABSTRACT

Objective: To compare the effects of resisted exercise in lungs volume and capacity and strength of the respiratory muscles on individuals with hemiparesis after a stroke.

Methods: Ten individuals with hemiparesis caused by stroke were evaluated by measuring thoracic cirtometry, spirometry and manovacuometry before and after a muscle strengthening program for upper and lower limb that consisted of three weekly sessions with progressive load increment (30, 40 and 50% of the maximum load). The pre and post intervention data were compared using the t-Student and Wilcoxon tests (p<0.05).

Results: The subjects assessed were 52.60±10.50 years old, 70% were men and 70% with right hemisphere damage. These are the pre and post intervention data concerning respectively to axillary thoracic mobility= 4.40±1.20 and 4.20±1.57 cm; xiphoid=4.45±1.34 and 4.90±1.76 cm; basal=4.00±1.68 and 4.25±2.52 cm, spirometry: FVC=3.52±0.57 L e 3.30±0.64 L; FVC%=93.06±9.77 e 86.81±14.06%; FEV1=2.72±0.49 L e 2.58±0.59 L; FEV1%=88.27±9.43 e 83.04±15.08%; Pimax=-88.50±24.27 e -91.50±21.09 cm H2O; Pemax = 96.00±23.78 e 95.50±15.71 cm H2O. After the training period with resisted exercise there was a statistically significant improvement on peripheral muscle strength (p<0.05). However, the variables associated with the respiratory function remained similar (p>0.05).

Conclusions: Adaptations caused by the resisted exercise training did not promote variation in thoracic expansion and respiratory muscles strength, as well as in lungs volume and capacity on subjects at a stroke chronic phase.

KEYWORDS: Respiratory mechanics; Stroke; Muscle strength; Physical therapy.

INTRODUCTION

Cerebrovascular diseases or stroke, main cause of permanent morbidity,1 were respon-
sible for close to 17 million deaths around the world in 2008. Damages caused by this disease include the plegias or paresis (uni or bilaterals), sensorial alterations and muscle tonus alterations. These changes are responsible for motor and functional deficits, that can compromise the respiratory biomechanics.

The respiratory damage shown by subjects after a stroke can result from motor and functional deficits, from the inadequate movement of the diaphragm and intercostal muscles of the affected hemibody, leading to a reduction of the maximum respiratory pressures, which indicates the reduction of the respiratory muscles strength.

Besides that, subjects who suffered a stroke can present reduction on the thoracic and pulmonary complacency, which leads to a reduction of the total lung capacity and vital capacity, pointing to a restrictive ventilatory disturb.

Rehabilitation programs after a stroke count on a great number of techniques which aim to improve the overall physical capacity. Besides that, it is well known that subjects with stroke effects must join muscle strength and aerobics conditioning programs to achieve functional improvements and also improvements on life quality, strength and physical conditioning.

On the other hand, the resisted exercises were, not long ago, contraindicated as a rehabilitation technique for subjects who suffered a stroke, due to the concern of exacerbating the spasticity. Recent studies have shown that resisted exercises do not change the spasticity, so it is getting more attention as a therapeutic resource for the neuromotor function. The main benefits of the resisted exercise are the improvements on muscle strength and resistance and the improvement on functional development without tonus alteration. According to Shepherd, muscle strengthening exercises act on increasing motor units recruitment, which improves body balance and both capacity and time of motor answer on generating strength. It also reduces the muscle stiffness and the reflexive hyperactivation while preserves the muscles functional extensibility.

We haven’t found in the literature, studies about the chronic effects of this kind of exercise over pulmonary functions on hemiparetic. On subjects with Chronic Obstructive Pulmonary Disease (COPD), the resisted physical exercise was effective in the improvement of the peripheral muscles strength and it can provide improvement of the Forced Vital Capacity (FVC), forced expiratory volume in the first second (FEV₁) and on the relation between both variables (FEV₁/FVC).

That said, the objective of this study was to investigate the effects of the training with resisted physical exercise over lungs volume and capacity and the respiratory muscles strength on subjects with hemiparesis after a stroke.

**MATERIALS AND METHODS**

**Design of Experiment**

After the approval of the Research Ethics Committee from the institution (document 0093/2011) a prospective and interventionist study was performed, where seventy volunteers were sorted after a previous diffusion of the research in health units, places with wide movement of people and local means of communication. Seventeen fulfilled the inclusion criterion and, among them, ten concluded the research protocol. The inclusion criterion were: (1) subjects over 18 years old, (2) unilateral cerebrovascular lesion, for at least six months, associated with hemiparesis, (3) ability to understand verbal instructions, (4) ability to stay in orthostatic position without auxiliary means, (5) no significant orthopedic and neurological alterations prior to the stroke. Subjects who were incapable of understanding or performing the required activities were not included. All the subjects who passed the inclusion criterion signed the Informed and Consent Form.

**Assessment**

The selected subjects undertook an assessment performed in three days. On the first day, anamnesis, body weight and height, cirtometry, spirometry and manovacuometry were performed. On the second and third assessment days, a one maximum repetition test (1RM) was performed and, after 72 hours, the muscle strengthening program for upper and lower limb started.

The body weight was performed on a digital weighing machine (Filizola® brand) and height was taken on a stadiometer device, attached to the weighing machine. The Body Mass Index (BMI) was calculated with these data by dividing the body weight (kg) by the squared height (m²).

For the thoracic cirtometry, the subject stood up straight with the upper limbs extended along the body. A measuring tape was used to measure the axillary, xiphoid and basal regions. Each measurement was taken after a maximum expiration, followed by a maximum inspiration and another maximum expiration. The difference between the maximum inspiration and expiration was taken as the thoracic expansibility. Measurements were repeated twice in each region, and only the highest values were considered.

The spirometry was performed according to the criteria of the American Thoracic Society (ATS), on a spirometer (Digital One Flow FVC Kit Function System 1070) and three forced vital capacity tests were performed, reproductive and acceptable. The FVC and FEV₁ in liters and the predicted percentage were obtained as well as the relation FVC/FEV₁ in percentage.

The assessment of the respiratory muscles strength was carried out using the maximum inspiratory and expiratory pres-
sure measures, MIP and MEP. The patient remained seated, with hips on 90° and straight stem. Nares were occluded by a nasal clip and the same was done with the mouth between teeth and lips, in order to avoid air escape. A forced inspiration from the residual volume was requested to obtain MIP and a forced expiration from the total lungs capacity was requested to obtain MEP. The procedures were repeated three times and the highest value was considered for the analysis.\(^{18}\)

In order to perform the training program, a one maximum repetition test (1RM) was performed with progressive load increment until obtaining the highest dislocated load on the total articular range in the eccentric and concentric phases, without support in all the exercises.\(^{19}\) The following muscle groups were tested: elbow flexors and extensors, shoulder horizontal adductors and abductors, shoulder abductors, knee flexors and extensors, hip flexors and extensors. The maximum strength tests were performed in two days; five exercises a day, randomly chosen, starting on the paretic and non paretic sides. Upper limb exercises were interspersed with lower limb exercises.

Muscle Strengthening Program

The training program was conducted in three weekly sessions for twelve weeks. The program consisted of exercises performed on an opened kinetic chain using mechano-therapy equipments: elbow flexion (biceps curl bench and dumbbells); elbow extension (dumbbells); shoulder horizontal adduction (pec deck); shoulder horizontal abduction (reverse pec deck); shoulder abduction (dumb bells); knee flexion (leg extension machine); knee extension (leg extension machine); hip adduction (adduction/abduction machine) and hip abduction (adduction/abduction machine), performed unilaterally (paretic side). In the first week, the training was performed with 30% of 1RM, in the second week 40% and in the following weeks 50% of 1RM. In the end of each month, the volunteers took the 1RM test again and the training loads were adjusted. A five-minute warm up was performed before every resisted training. After the trainings, also in every session, there was a 5 minute relaxation.

Blood pressure and heart rate were monitored in the beginning and in the end of the sessions. After performing the training protocol, patients were reassessed.

Statistical Analysis

The descriptive statistics was used for the characterization of the sample and data presented in mean and standard deviation. The variables went through a Shapiro–Wilk normality test. The ones which presented normal distribution were compared with a t-student test and those which didn’t present normal distribution were compared with a Wilcoxon test, with a 5% level of significance. The statistical software BioEstat 5.0 was used for all the analysis.

RESULTS

Ten subjects were assessed, 70% of them were men. They were 52.60±10.50 years old, they had 82.10±18.05 kg of body weight, 1.69±7.31 m of height and they also had 28.70±5.99 kg/m² of BMI. The cerebrovascular lesion time was 40.60±29.56 months, and 70% of them presented right hemiparesis.

The thoracic mobility, as well as the spirometric variables and maximum respiratory pressures didn’t show significant differences in the sample when compared to the assessments before and after the muscle strengthening program (Table 1).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before</th>
<th>After</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CaXillary (cm)</td>
<td>4.40±1.20</td>
<td>4.20±1.57</td>
<td>0.34</td>
</tr>
<tr>
<td>Cxipoid (cm)</td>
<td>4.45±1.34</td>
<td>4.90±1.76</td>
<td>0.09</td>
</tr>
<tr>
<td>Cbasal (cm)</td>
<td>4.00±1.68</td>
<td>4.25±2.52</td>
<td>0.33</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.52±0.57</td>
<td>3.30±0.64</td>
<td>0.06</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>93.06±9.77</td>
<td>86.81±14.06</td>
<td>0.06</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>2.72±0.49</td>
<td>2.58±0.59</td>
<td>0.08</td>
</tr>
<tr>
<td>FEV₁ (%)</td>
<td>88.27±9.43</td>
<td>83.04±15.08</td>
<td>0.07</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>83.62±10.62</td>
<td>78.70±13.74</td>
<td>0.09</td>
</tr>
<tr>
<td>MIP (cmH₂O)</td>
<td>-85.50±24.27</td>
<td>-91.50±21.09</td>
<td>0.24</td>
</tr>
<tr>
<td>MEP (cmH₂O)</td>
<td>96.00±23.78</td>
<td>95.50±15.71</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Table 1: Comparison of the variables before and after the muscle strengthening program.

On the 1RM test in the paretic side, there was improvement in every muscle group assessed, except on elbow and knee flexors and knee extensors (Table 2).

<table>
<thead>
<tr>
<th>Muscle Groups</th>
<th>Before</th>
<th>After</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbow flexors</td>
<td>5.50±3.72</td>
<td>7.22±4.68</td>
<td>0.09</td>
</tr>
<tr>
<td>Elbow extensors</td>
<td>3.20±2.86</td>
<td>4.44±2.13</td>
<td>0.03</td>
</tr>
<tr>
<td>Shoulder abductors</td>
<td>2.40±2.88</td>
<td>3.70±2.00</td>
<td>0.02</td>
</tr>
<tr>
<td>Horizontal abductors</td>
<td>12.50±10.61</td>
<td>17.50±13.59</td>
<td>0.02</td>
</tr>
<tr>
<td>Horizontal adductors</td>
<td>16.50±14.54</td>
<td>26.50±15.99</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Knee flexors</td>
<td>16.22±13.45</td>
<td>18.78±13.31</td>
<td>0.10</td>
</tr>
<tr>
<td>Knee extensors</td>
<td>7.00±4.38</td>
<td>8.13±4.58</td>
<td>0.20</td>
</tr>
<tr>
<td>Hip abductors</td>
<td>34.00±19.26</td>
<td>44.50±18.33</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hip adductors</td>
<td>47.00±24.97</td>
<td>58.00±21.37</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Table 2: Comparison of the 1RM test in kilograms on the paretic side, before and after the muscle strengthening program.
In the non paretic side there was improvement on elbow flexors and extensors and hip abductors (Table 3).

Table 3: Comparison of the 1RM test in kilograms on the non paretic side, before and after the muscle strengthening program.

<table>
<thead>
<tr>
<th>Muscle Groups</th>
<th>Before</th>
<th>After</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbow flexors</td>
<td>10.50±4.45</td>
<td>12.11±5.11</td>
<td>0.02</td>
</tr>
<tr>
<td>Elbow extensors</td>
<td>8.70±2.75</td>
<td>7.56±2.83</td>
<td>0.01</td>
</tr>
<tr>
<td>Shoulder abductors</td>
<td>5.20±2.15</td>
<td>5.20±1.87</td>
<td>0.50</td>
</tr>
<tr>
<td>Horizontal abductors</td>
<td>25.50±7.62</td>
<td>29.50±11.41</td>
<td>0.07</td>
</tr>
<tr>
<td>Horizontal adductors</td>
<td>29.00±9.66</td>
<td>28.00±12.29</td>
<td>0.38</td>
</tr>
<tr>
<td>Knee flexors</td>
<td>19.50±13.01</td>
<td>20.50±11.65</td>
<td>0.17</td>
</tr>
<tr>
<td>Knee extensors</td>
<td>12.50±6.77</td>
<td>13.00±6.32</td>
<td>0.29</td>
</tr>
<tr>
<td>Hip abductors</td>
<td>39.00±20.39</td>
<td>44.50±18.17</td>
<td>0.02</td>
</tr>
<tr>
<td>Hip adductors</td>
<td>57.00±20.84</td>
<td>56.50±19.30</td>
<td>0.36</td>
</tr>
</tbody>
</table>

DISCUSSION

Analyzing the effects of the resisted exercise in the studied variables, no significant differences were found in thoracic mobility as well as in lungs volume and capacity and strength of the respiratory muscles, even though there was improvement in the muscle groups trained.

The studied sample was composed, in its majority, by male subjects, which confirms studies that point to a greater stroke incidence on men. Concerning age, the mean was 52.60±10.50 years old, indicating that the studied sample can suffer the aging harmful effects besides the hemiparesis that can interfere in a negative way in the variables after the muscle strengthening. It’s known that aging leads to a reduction in innervation, capilar density, number and size of muscle fibers and therefore substitution of the muscle tissue for non contractile tissue, bringing reduction on peripheral muscle strength and less fatigue resistance. These factors may have interfered on muscle strength gain in lower limbs in this sample.

Concerning the respiratory system, studies show that aging leads to a reduction in the number of alveolus and pulmonary compliance, raise in thoracic anteroposterior diameter and thoracic kiphosis in a way that there is a reduction in the pulmonary function. The majority of the subjects were over 50 years old, besides that, we believe that age hasn’t influenced the results of pulmonary function since all of them were according to the normality parameters.

The majority of subjects showed right-sided hemiparesis indicating left-sided cerebral lesion. There is no consensus in the literature about the most affected hemisphere. What is known is that the left hemisphere is dominant for the motor control, that is, motor activities are more damaged in subjects with left-sided lesion, suggesting that these subjects present a lower functional recovery when comparing to subjects with right-sided lesion. As the sample was mostly composed by subjects with left-sided cerebral lesion, we believe that the damaged hemisphere may have been one of the factors that contributed to our results, as well as the training applied, which didn’t aim the respiratory muscles specifically.

Thoracic expansibility alteration allows us to infer that there is also change in the volume of mobilized air during respiration. Thus, the asymmetry in the respiratory dynamics, as it happens in the hemiparesis, is going to lead to a reduction in the thoracic mobility because of the movement restriction of the paretic hemithorax, being the lower thoracic region the most restricted. The reference values for the thoracic cirtometry vary between 4 to 11 centimeters. In this study, subjects presented less than 4 centimeters of mean in the thoracic basal region. Other assessed regions showed thoracic expansibility close to 4 centimeters. The thoracic expansibility didn’t show significant difference after the training program, which is attributed to the non significant alteration of the respiratory muscles strength, which would lead to a lung volume increment. In the sample, as there was no significant increment in the strength of the respiratory muscles, the thoracic expansibility also didn’t show significant alteration after the muscle strengthening program.

The analysis of the spirometric variables before the program indicates that the sample presents normal values, which goes against the literature information that shows that hemiparetic individuals present pulmonary ventilatory restrictive defect, characterized by a reduction of FVC and FEV1 with FEV1 / FVC values close to the normality. After the muscle strengthening, there was no significant alteration of lungs volume and capacity, besides the reduction in the thoracic expansibility when compared to the normality. The strength of the respiratory muscles can also have interfered on lungs capacity and volume during the FVC test.

Concerning strength of the respiratory muscles, the obtained values were according to the normality, which can be justified by the compensation strategies to maintain pulmonary function that are developed by individuals with chronic hemiparesis, such as higher muscle recruitment on the non paretic side and use of accessory muscles. In the present study, the maximum respiratory pressures showed a slight increment after the muscle strengthening program, but this value was not statistically relevant. The muscle training program performed didn’t aim specifically the increment of the respiratory muscles strength and, even though it involved the scapular waist muscle, it was not able to change the strength of the respiratory muscles in a significant way. It’s important to highlight that the resisted exercise didn’t influence, in a positive or negative way, the studied variable. Thus, there’s no risk of exacerbating the chronic respiratory damages of individuals with hemiparesis.

While analyzing the peripheral muscle strength before and after the muscle strengthening training, it was possible to
find a strength gain in all muscle groups involved, even though it was slight and not significant in some muscle groups, suggesting that the work load used in the protocol may have been underestimated. According to Hill, et al. the strengthening training with load between 85% and 95% of the 1RM increases significantly the muscle strength and the performance of hemiparetic individuals on the Six Minute Walk Test (6MWT). In our study, the loads used were 30%, 40% and 50% of the 1RM, which is relatively low when compared to the study quoted above. Besides that, we used static tests to assess pulmonary function. The use of the 6MWT would allow us to check if the used loads were capable of providing improvements in the cardiopulmonary capacity, even though the pulmonary function, individually, was not significantly changed.

Though we have observed an increment on strength in muscles related to the scapular waist, which could influence the respiratory mechanics, this improvement was not enough to change the respiratory parameters. Protocols focused on the strengthening of the stem muscles and respiratory muscles are necessary in order to obtain significant results when it comes to respiratory muscles strength.

The significant increment of the peripheral muscle strength in the majority of the muscle groups assessed in the paretic side, and in some groups of the non paretic side, can indicate benefits of the resisted exercise by suggesting adaptations in the neuromuscular system, higher recruitment of motor units and discharge synchronization, sparking bilateral stimulus.

In our study, in the lower limbs groups of muscles, there was no significant strength increment on both paretic and non paretic sides, which explains the non significant change in the pulmonary function of the subjects since the study showed that the positioning adopted during the strengthening exercise of the lower limbs, that demands activity from the abdominal muscles, can influence the forced expiration.

New studies must be done with higher work load, exercises focused on the respiratory muscles and using other tests that assess the cardiorespiratory function, which will allow the assessment of whether the muscle strengthening provides functional capacity improvement. Even though the sample studied in this work presents diversity when it comes to lesion time, we believe that this variable didn’t influence the results, as all participants had unilateral cerebrovascular lesion for, at least, six months, which is the period of time to consider the hemiparesis chronicity. It is important to highlight that overall, seventy volunteers were sorted. However, only seventeen did not present plegia in any body segment and could perform the movements required during the performance of the training program. Thus, the sample was considered homogeneous for the level of musculoskeletal compromising. From the seventeen participants, seven were not included for not taking the twelve week training.

The results of the present study indicate that the adaptations caused by the training with resisted exercise did not promote alterations in the thoracic expansibility and strength of the respiratory muscles, as well as in the lungs volume and capacity of individuals at a stroke chronic phase.

CONFLICTS OF INTEREST: None.

REFERENCES


