行政院國家科學委員會專題研究計畫　成果報告

吸氣肌訓練對於慢性阻塞性肺部疾病患者的下肢血流及運動功能效果之研究

計畫類別：個別型計畫
計畫編號：NSC91-2314-B-002-363-
執行期間：91年08月01日至92年12月31日
執行單位：國立臺灣大學醫學院物理治療學系暨研究所

計畫主持人：王儷穎

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報告類型：精簡報告
報告附件：出席國際會議研究心得報告及發表論文
處理方式：本計畫可公開查詢

中　華　民　國 93年5月10日

附件一

行政院國家科學委員會補助專題研究計畫

▒成果報告
□期中進度報告

吸氣肌訓練對於慢性阻塞性肺部疾病患者下肢血流及運動功能效果之研究

Effects of inspiratory muscle training on lower limb blood flow and exercise capacity in patients with COPD

計畫類別：▒個別型計畫　　□ 整合型計畫
計畫編號：NSC 91－2314－B－002－363－
執行期間：91 年 08 月 01 日至 92 年 12 月 31 日

計畫主持人：王儷穎
共同主持人：吳英黛
計畫參與人員：吳惠東、簡盟月

成果報告類型(依經費核定清單規定繳交)：▒精簡報告　□完整報告

本成果報告包括以下應繳交之附件：
□赴國外出差或研習心得報告一份
□赴大陸地區出差或研習心得報告一份
□出席國際學術會議心得報告及發表之論文各一份
□國際合作研究計畫國外研究報告書一份

處理方式：除產學合作研究計畫、提升產業技術及人才培育研

計畫、列管計畫及下列情形者外，得立即公開查詢
□涉及專利或其他智慧財產權，□一年□二年後可公開查詢

執行單位：國立台灣大學醫學院物理治療學系暨研究所

中　華　民　國　93 年　　3　月　　1　日

ABSTRACT

Exercise capacity and tolerance are often limited in patients with COPD due to dyspnea. Recent studies have shown that the reduced exercise capacity might be related to limited blood flow and oxygen (O_2) supply to exercising muscles due to redistribution of blood flow to inspiratory muscle. We hypothesized that inspiratory muscle training (IMT) would redistribute blood flow and O_2 supply from the inspiratory muscle at any given level of exercise to the leg muscles and which in turn would increase exercise performance and lower lef blood flow during cycling exercise. 30 patients with moderate to severe COPD ($FEV_1/FVC < 70\%$, $FEV_1 < 50\%$ predicted) were recruited for the study. Subjects received home-based IMT with a threshold loaded breathing device 5 minutes for 3 times a day, 5 days a week for 8 weeks. Incremental exercise test and 6-minute walk test were done before, and at the end of the training sessions. Before the exercise test, subjects performed spirometry and inspiratory muscle strength and endurance were measured. During incremental exercise test, ventilatory parameters (eg., tidal volume (V_t), breathing frequency (f), and minute ventilation (V_E)), oxygen consumption (VO_2) and time to exhaustion were measured. Borg Category-Ratio Scale was used to measure dyspnea at the end of each minute of exercise. Leg blood flow was determined by the laser Doppler technique (DRT4, Moor Instrument, UK). Quality of life was assessed by WHOQOL-BREF. In patients with moderate to severe COPD, 8 weeks of home-based IMT 1) increased both P_{Imax} and P_{Emax}, 2) increased VO_{2peak}, W_{paek}, 6MWD, and 6MWW, 3) increased Physics domain score of WHOQOL-BREF, and 4) lower leg BF decreased at rest and increased during cycling exercise at 50W. Although LDF is a safe and non-invasive measuring option, our data are preliminary and further explosion of the validity of this method is needed.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. In 2002, COPD is the eleventh leading causes of death in Taiwan, and the projected cost of cares is NT$39 billion.(1) Exercise capacity is often impaired in patients with COPD and has a great impact on health-related quality of life.

Exercise limitation in patients with COPD is complex and multifactorial. Weakness and deconditionized of both respiratory and peripheral muscles are currently recognized in patients with COPD.(2) Patients with advanced COPD were presumed to have a ventilatory limitation to exercise, i.e., exercise was terminated due to disabling dyspnea before the exercising muscles were stressed very much.(3) Theoretically, the high demand for oxygen and blood flow by the respiratory muscles during exercise in COPD patients and thus the available blood flow is reduced to exercising locomotor muscles.

Previous studies have demonstrated that inspiratory muscle training (IMT) induces a specific functional improvement of the inspiratory muscle (strength and/or endurance) and is an important addition to a pulmonary rehabilitation program for patients with COPD.(4, 5) Theoretically, at a given level of exercise, if metabolic demand of the respiratory muscle could be reduced after IMT, more blood flow could be directed to the exercising muscle, and thus increases the exercise capacity. The aim of this study was to determine if IMT alone could enhance exercise capacity and endurance and decrease rating of perceived leg fatigue during cycling exercise in moderate to severe COPD patients.

METHODS

Subjects:

Thirty patients between 60 and 75 years of age with moderate-to severe COPD volunteered to participate in this study. All patients were initially screened for study eligibility by a chest physician. The subject inclusion criteria for the study were: 1) between 50 and 80 years of age; 2) severity of stage II ($FEV_1/FVC < 70\%$、$50\% \leq FEV_1 \leq 80\%$ predicted) or III ($FEV_1/FVC < 70\%$、$30\% \leq FEV_1 \leq 50\%$ predicted) COPD according to the recently published guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD);(6) 3) capable of undergoing exercise testing to peak effort; and 4) all participants were in the stable phase of their disease and were receiving a stable medication regimen. Participants with coexisting medical conditions (e.g., cardiac or musculoskeletal disorders) that would interfere with exercise tests were excluded from the study. The study was approved by the Institutional Review Board of the National Taiwan University Hospital, and written informed consent was obtained from all subjects.

Body composition

Body weight and height were measured anthropometrically. Body mass index (BMI) was calculated by dividing whole body weight in kilograms by the squared body height in meters. Fat-free mass (FFM) was assessed by bioelectrical impedance method (BIA Spectrum III, RJL Systems, Detroit, MI). Resistance was measured in supine position at the right side as described by Lukaski et al.(7) The FFM index (FFMI) was calculated by dividing the FFM by the squared body height in meters to correct for differences in body size.(8)

Spirometry

Spirometry was done in the sitting position with a computerized SensorMedics Vmax 29 system (SensorMedics, Yorba Linda, CA 92887). Spirometry test was performed according to the standards outlined by the American Thoracic Society (ATS) criteria.(9) The best flow-volume loop was used in the final analysis of the data. Forced vital capacity (FVC), and forced expiratory volume in one second (FEV_1) were measured and the ratio of FEV_1 to FVC was calculated. Normal predicted spirometric values were derived from the equations of Yang (for Chinese men).(10) Maximal inspiratory pressure (P_{Imax}) was defined as the maximal negative pressure that could be generated at the mouth from the residual volume and sustained for at least 1 second.(11) An aneroid inspiratory force meter (Model 4103, Boehringer Laboratories Inc, Norristown, PA 19404) with a cylindrical mouthpiece was used for measurements. The respiratory muscle endurance was defined as the maximal time that the subjects could breathe against 70% P_{Imax}(11) using a threshold inspiratory muscle training device (No 730 Threshold, Healthdyne Technologies Inc, NJ 07009).

Submaximal exercise test: Six-minute walk test (6MWT)

The 6-min walk test was conducted according to a standardized protocol.(12) Subjects was instructed to walk from one end to the other of a 50 m hallway at their own pace, while attempting to cover as much ground as possible in the allotted 6 min. The standardized statements “You are doing well” or “Keep up the good work” were used to encourage subjects. Subjects were allowed to stop and rest during the tests, and will resume walking as soon as they feel able to do so. Dyspnea, as measured with the Borg dyspnea scale, ranged 0-10, with “no breathlessness” at one end of the scale and “greatest breathlessness that you have experienced” at the other end,(13) oxygen saturation (SpO_2), and heart rate (HR) were measured at the start and end of the test. At the end of the test, the total distance walked (6MWD) was recorded. The 6-minute walk work (6MWD×W) was calculated by multiplying distance walked in kilometers by the body weight in kilograms.(14) Percent predicted 6MWD was calculated based on the reference equations of Enright and Sherrill.(15)

Graded Exercise Test (GXT)

The incremental symptom-limited exercise test was performed on an electrically braked cycle ergometer (Ergometrics 800, SensorMedics, Yorba Linda, CA 92887). After 3 minutes of unloaded pedaling for warm-up, work rate was increased by 25 watts every 3 minutes until volitional termination or when the subject could no longer sustain the pedaling rate between 50 to 60 rpm with encouragement. Cycling cadence was maintained at 60 revolutions per minute (rpm). Both inspiratory and expiratory airflow were obtained from the calibrated mass flow sensor (Vmax29 Metabolic Measurement System, SensorMedics, Yorba Linda, CA 92887) and electronically integrated to obtain volume measurements. Respiratory gases were measured at the mouthpiece, with oxygen uptake (VO_2) measured at rest and during exercise by use of an on-line breath-by-breath system. All test results were stored for subsequent analysis. During the test, oxygen saturation (SpO_2) was monitored continuously with a pulse oximeter (S-100, SiMed Corp, Bothell, WA 98011). Breath by breath values for tidal volume (V_T), breathing frequency (F_b), minute ventilation (V_E), and heart rate (HR) were averaged fro each minute of exercise. Peak oxygen consumption (VO_{2peak}) and power output (W_{peak}) were measured at the moment of cessation of the exercise. Normal predicted values were computed according to the method of Jones et al (16) for maximal oxygen uptake (VO_{2max}) and power output (W_{max}).

Laser Doppler Flowmetry

Low leg blood flow was measured with a high power laser Doppler source (20 mW, emitting wavelength 780nm) in combination with a conventional laser Doppler flowmeter (DRT4, Moor instruments, Axminster, England). Higher energy and increased distance between emitting and receiving fibers (10 mm) resulted in better signal to noise ratio. Medical gastrocnemius (MG) muscle of the right leg was used to assess the lower-leg blood flow during cycling exercise. The leg’s circumference was measured at 1/3 of the distance from the fibular head to the lateral malleolus. The emitting probe was fixed at this level after moving medially from the tibial crest by 1/3 of the leg’s circumference, and the receiving probe was fixed 2 cm longitudinally down from the emitting probe. The reflected light is amplified by an analogue processor (mV) and thereafter digitally processed. Blood flow (BF) was measured in FLUX units, which is the product of concentration and velocity of erythrocytes within the volume beneath the probe. FLUX was described in arbitrary unit (AU), which are defined by calibration against a standard reference of polystyrene microspheres, as provided by the manufacturer. The signals were continuously recorded in real time and stored for later analysis on a DRT4 Windows computer software program (software version 1.0). The time constant was set at 0.1s and the display rate was set at 20 s-1 to enable the visualization of pulsatile signals, e.g. signal amplitudes synchronous to the heart rate as checked by ECG. Mean values and standard deviation of the waves were calculated during a period of at least 10s after the signal has stabilized.

Inspiratory muscle training

Patients trained with a threshold loaded breathing device (Threshold IMT Inspiratory Muscle Trainer; HealthScan, Cedar Grove, NJ). The inspiratory orifice of this device is occluded with a spring-loaded poppet valve and the inspiratory pressure load is adjusted by varying the compression of the spring. Stiffer or limper springs were used as needed to establish the appropriate inspiratory pressure load. Patients trained 5 d/wk, 30 min/d for 8 weeks. The training was initiated at an intensity equal to 30% of maximal inspiratory pressure (P_{Imax}) with progressive increases as tolerated up to 60% of the current P_{Imax}. An interval training protocol was used with patients performing 6 work sets, 5 min in duration, separated by rest intervals lasting 1-3 min. Patients kept a log for their IMT and biweekly home visits and weekly phone contact were made by a physical therapist to monitor training and adjust the training load.

Quality of Life

The health-related quality of life was measured by the brief version of the World Health Organization's Quality of Life (WHOQOL-BREF) which contains two items from the Overall Quality of Life and General Health facet and one item from each of the remaining 24 facets (17). WHOQOL-BREF assesses four domains of quality of life: Physical Capacity, Psychological Well-being, Social Relationships, and Environment. The Taiwanese version includes two additional items of local importance, i.e., being respected and food availability in Social Relationships Environment domains, respectively.(18) The reliability and validity of this version have been reported to be good.(18) Higher scores correspond to better health-related quality of life.

Data & Statistical Analysis

All statistical analyses were performed with the SigmaStat statistical software (version 3.00, SPSS Inc, Chicago, IL 60606). Results are expressed as mean (± SE).

P value less than 0.05 was considered significant. We used a two-way analysis of variance with repeated measurements followed by a Bonferroni t-test post-hoc procedure to determine the statistical significance of differences between pre- and post-IMT training. The criteria for statistical significance was established at P<0.05.

RESULTS

Anthropometric and spirometry data for all the subjects are presented in Table 1. Disease severity of the subjects ranged from moderate (27%; 8/30) to severe (73%; 22/30) airway obstruction with an average percentage of predicted FEV_1 values of 40.50% (range 34-66%). The subjects were either normal weight (10/30) or under weight (20/30) with a mean BMI of 20.8 kg/m^2 (range 15.7-25.8 kg/m^2) and a FFMI of 18.7 kg/m^2 (range 15.5-20.3 kg/m^2). The mean body weight, BMI, and FFMI remained unchanged after 8 weeks of IMT training.

The prescribed IMT load increased from a mean of 30.5 (±7.8) % at the start of the study to a mean of 60.8±15.2% of baseline P_{Imax} (which represented 52±8% of the current P_{Imax}) during the last week of the IMT training. From the training log, the calculated mean IMT training hours was 1084.6 (±28.9) hours (target was 1200 hours), this suggested a good adherence to IMT.

Outcomes of respiratory muscle function are presented in Table 1. After 8 weeks of IMT training, P_{Imax} increased by 19% ($P<0.001$) and P_{Emax} increased by 13% ($P<0.05$) compared to pre-IMT training baseline.

The physiological responses of the GXT are shown in Table 2. The mean VO_{2peak} during GXT was 15.1 (±3.5) and 16.8 (±2.6) mL/kg/min for pre- and post-IMT training, respectively, and they represented 49.9 (±19.2)% and 57.9 (±16.7)% ($p<0.05$) of the predicted VO_{2max}, respectively. The mean W_{peak} also increased significantly from 55.5 (±19.1) at pre-IMT training baseline to 70 (±19.4) watts post 8 weeks IMT training. The average peak V_E, f, V_T, and RER during GXT were not different between baseline and post IMT training. The mean peak HR increased significantly from baseline to post IMT training. The end point of the exercise test for all the subjects was severe dyspnea with Borg dyspnea score of 9-10, and the mean changes in Borg score from the end of the test to resting were similar between pre- and post-IMT training.

Table 3 shows the physiological changes in response to 6MWT for pre- and post IMT training. The mean 6MWD increased significantly from pre-IMT training of 328.08 (±33.11) to 403.17 (±37.20) m post-IMT training, and they represented 75.6 and 82.4 % of the predicted 6MWD, respectively. Changes in SpO_2, HR and Borg score during 6MWT were not different between pre- and post IMT training. The mean 6MWW increased significantly from pre-training of 19.66 (±9.22) to 24.57

(±6.26) km-kg of post-IMT training.

The initial output signal was pulsatile in all patients. At rest, lower leg BF decreased significantly from pre-IMT training of 27.17 (±9.23) to 22.23 (±10.2) AU post-IMT training. During GXT, lower leg BF at 50W increased significantly from 29.78 (±12.14) pre- to 47.23 (±13.77) AU post-IMT training.

The mean domain scores of WHOQOL-BREF for all patients are listed in Table 5. The only domain which showed significantly improvement after IMT training was Physics (pre of 12.67±12.14 vs. post of 13.83±1.64). The mean scores of the remaining 3 domains were not different between pre- and post-IMT training measurements.

Table 1. Anthropometric and spirometry data for all COPD patients studied

Variables	Pre-training	Post-training
Age, yr	67.00 ± 5.33	
Smoking history, yr	36.7 ± 2.7	
Energy expenditure	2036.3 ± 488.8	2081.4 ± 326.8
Weight, kg	58.9 ± 12.8	60.3 ± 13.8
Height, cm	163.6 ± 3.4	163.6 ± 3.4
BMI, kg/m^2	20.8 ± 3.2	21.2 ± 4.1
FFMI, kg/m^2	18.7 ± 2.5	19.2 ± 1.8
FEV_1, L	1.02 ± 0.27	1.25 ± 0.39*
FEV_1 , % predicted	40.50 ± 10.00	49.50 ± 14.04*
FVC, L	2.62 ± 0.65	2.71 ± 0.59*
FVC, % predicted	72.67 ± 17.32	75.33 ± 15.58*
Pi_{max}	44.1 ± 10.5	52.6 ± 10.2*
Pe_{max}	40.1± 9.6	45.5 ± 5.1*
Endurance	103.5 ± 120.2	220.67 ± 198.1*

Values given as group means ± SD.

BMI, body mass index; FFMI, fat-free mass index; FEV_1, forced expiratory volume in one second; and FVC, forced vital capacity.

Table 2. Physiological responses of the graded exercise test.

Variables	Pre-training	Post-training
VO_{2peak}, mL/kg/min	15.1 ± 3.5	16.8 ± 2.6*
VO_{2peak}, % predicted	49.9 ± 19.2	57.9 ± 16.7*
W_{peak}, watts	55.50 ± 19.06	70.0 ± 19.4*
W_{peak}, % predicted	41.4 ± 17.3	51.9 ± 15.7*
$V_{E\ peak}$, L/min	37.55 ± 10.41	38.28 ± 9.78

f_{peak}, breaths/min	31.80 ± 3.49	33.00 ± 2.91
$V_{T\,peak}$, L/min	0.58 ± 0.12	0.90 ± 0.14
HR_{peak}, bpm	128.4 ± 16.8	137.4 ± 12.5*
RER	1.02 ± 0.32	1.03 ± 0.35
Change in Borg score	8.07 ± 1.63	8.67 ± 1.32

Values given as group means ± SD.

VO_{2peak}, peak oxygen consumption; W_{peak}, peak power output; $V_{E\,peak}$, peak minute ventilation; f_{peak}, peak breathing frequency; $V_{T\,peak}$, peak tidal volume; HR_{peak}, peak heart rate; RER: respiratory exchange ratio.

Table 3. Physiological changes of the six-minute walk test

Variables	Pre-training	Post-training
6MWD, m	328.08 ± 33.11	403.17 ± 37.20*
6MWD, % predicted	75.6 ± 14.9	82.4 ± 8.5*
6MWD*W, km-kg	19.66 ± 9.22	24.57 ± 6.26*
HRpre, bpm	100.33 ± 5.84	96.83 ± 8.88
HRpost, bpm	107.67 ± 18.29	106.5 ± 18.40
SpO_2 pre, %	94.0± 2.4	95.17 ± 1.4
SpO_2 post, %	92.0 ± 2.8	93.4 ± 2.99
Borg dyspnea score (end-rest)	1.33 ± 1.02	1.73± 1.03

* indicates $p<0.05$.

6MWD, distance walked in six minute; 6MWD×W, distance walked times body weight; and SpO_2, pulse oxygen saturation.

Table 4. Blood flow changes of the graded exercise test

Variables	Pre-training	Post-training
BF_{rest}	25.02 ± 10.09	22.23 ± 10.20*
BF_{50watt}	29.78 ± 12.14	47.23 ± 13.77*

* indicates $p<0.05$.

BF, peripheral blood flow.

Table 5. Quality of life changes

Domaim	Pre-training	Post-training
Physics	12.67 ± 1.87	13.83 ± 1.64*
Psych	12.00 ± 1.47	12.33 ± 1.56
Social	13.17 ± 2.59	14.50 ± 2.68*

Social modify	13.67 ± 2.06	14.67 ± 2.39
Environment	14.00 ± 1.21	14.50 ± 1.98
Environment modify	14.42 ± 1.08	14.83 ± 1.75

* indicates p<0.05.

Score range from 4 to 20.

DISCUSSION

The results of this study demonstrated that in patients with moderate to severe COPD, 8 weeks of home-based IMT 1) increased both P_{Imax} and P_{Emax}, 2) could produce physiological training effects as reflected by increases in VO_{2peak}, W_{paek}, 6MWD, and 6MWW, 3) increased Physics domain score of WHOQOL-BREF, and 4) lower leg BF decreased at rest and increased during cycling exercise at 50W.

Many factors may affect the LDF measurement. It depends on the features of the examined tissue: its anatomical character, microvascular architecture, dehydration,. Of the affected surface, body posture, sex, age, hormonal. Neuronal, and pharmaceutical effects. Some changes in instrument parameters such as contamination of the measuring probe and rupture or stretch in the optical fiber. During examinations, it is essential to obtain a stable measurement, minimizing the artifacts in the recorded signal data due to, for example, muscle and respiratory movements. In this study, we used the custom-made probe holders to deal with the problem of the coupling of the laser Doppler probes to skin. Our recent measurements have some disadvantages. First, the tests were performed on the skin and the exact depth of laser beam penetration was unknown and the affect of the subcutaneous tissue could not be ruled out. Secondly, according to the stable measuring principle, dynamic measurements (e.g., during exercise) was not possible using LDF. Although LDF is a safe and non-invasive measuring option, our data are preliminary and further explosion of the validity of this method is needed.

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