Effects of Exercise Training on Surgery Tolerability in Lung Cancer Patients with Impaired Pulmonary Function

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Abstract: To investigate effects of preoperative, short-term and medium and high strength exercise training of lower limbs on tolerance of lung resection operation in lung cancer patients with impaired pulmonary function. 61 patients were divided into the operation group A (44) and the non-operation group B (17) randomly according to the American Society of Thoracic Surgeons. The group A was randomly divided into A1 (22) and A2 (22) group. Treadmill training combined with thoraco-abdominal pursed lip breathing training were conducted in the A1 and the group B. The static lung function and cardiopulmonary exercise function were tested. Heart and lung function index including forced vital capacity, minute ventilation volume, diffusion capacity for CO of lung, the maximum power load, VO2max, anaerobic threshold, oxygen pulse VO2max/HR, peak ventilation, dyspnea index, CO2 equivalent when it is anaerobic threshold VE/VCO2@AT and transcutaneous oxygen saturation after exercise SPO2% ($P < 0.05$) all significantly improved after exercise. Recovery time after lung resection, mechanical ventilation time, and hospitalization days have significantly diffirence between A1 and A2 group ($P < 0.05$). Preoperative, short-term and medium and high strength exercise training can effectively and feasibly enhances adaptability of cardiopulmonary functions.

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1. Introduction

Pulmonary resection is the first and effective treatment method of non small cell lung cancer. Chronic obstructive pulmonary disease (COPD) in many resectable lung cancer patients results in significantly impaired lung function. Risks of complications after lung resection increase, and lung cancer patients even lose chances of radical resection of lung cancer. Therefore, how to improve surgery tolerance of lung cancer patients with low lung function is a problem that to be solved immediately.

Based on the pulmonary resection preoperative evaluation model of resting pulmonary function-pulmonary radionuclide perfusion scan-cardiopulmonary exercise test, exercise maximal oxygen uptake (VO2 max) has been confirmed to be a strong and effective predicting factor of operation complication risk [1]. If preoperative VO2max is increased by reasonable exercise training, operation tolerable ability can be improved and risks of postoperative complications can be reduced.

In the present study, effects of mainly preoperative, short-term and medium and high strength exercise training of lower limbs and additionally short-term pulmonary rehabilitation of respiratory muscle training on tolerance of lung resection operation in COPD and lung cancer patients with impaired pulmonary function were investigated.

1.1 Subjects and methods

1.1.1 Subjects

Sixty-one lung cancer patients were collected and confirmed in Cancer center of Sun Yat-sen University from January of 2009 to December of 2011. The pulmonary resection was the first treatment choice with all patients in accordance with the inclusion criteria. Preoperative resting pulmonary function test (Italia COSMED, Quark PFT4 Pulmonary function instrument.) confirmed that they were combined severe COPD with the forced expiratory volume at 1st second (FEV1) among 30%-50% of normal prediction value [2]. There was no severe and acute complication of uncontrollable high pressure, diseases of heart, lung, liver and kidney. There was no exercise contraindication [3]. The patient trainers agreed and signed the informed consent. Research program was approved by the Sun Yat-sen University cancer prevention center ethics committee.

2. Methods

2.1 Grouping

All patients were subjected to pulmonary radionuclide perfusion scan analysis using the STARCAM3200Z scanner (America) and the first and maximum symptom-limited cardiopulmonary exercise test (Italia COSMED, Quark PFT4 Pulmonary function instrument.) [3]. According to the American Medical Association (ACCP) guidelines of 2007 [1], predictive postoperative lung function values (ppo) = preoperative lung function value ×（1- percentage of the resected pulmonary segments in the ipsilateral lung segments × percentage of quantity of ipsilateral pulmonary radionuclide perfusion in the quantity of the total pulmonary radionuclide perfusion. When ppo-FEV1% < 30% or ppo-FEV1% × ppo-DLCO% < 1650% or VO2max < 10ml/kg/min, it was not feasible to conduct pneumonectomy, and patients were divided into the operation group A (44 cases) and the non-operation group B (17 cases). The group A (22 cases) was randomly divided into the exercise subsection A1 and the control group A2 (22 cases). There was no statistical difference in respect to gender, ages, body weight index, smoking, pathological types, tumor TNM stages, complication diseases and preoperative pulmonary function evaluation ($P > 0.1$) (Table 1) between the group A1 and the group A2. The group B and the subsection A1 (39 cases) were subjected to exercise training.

Table 1. Comparison indice in the exercise subsection A1 and the control A2 before operation

variable	The subsection group A1 (n=22)	The control group A2 (n=22)	χ^2/t	*P* value
Men(n) ages	18	16	0.518	0.472
(years) body	59.1±9.4	60.3±11.0	0.389	0.699
weight index(kg/m^2)	24.2±3.2	23.9±2.9	0.326	0.746
smoking index (year×1/day)	65.3±10.2	66.1±10.6	0.255	0.800
complications			0.493	0.920
High pressure diseases(n)	10	12		
coronary disease（n）	5	4		
Diabetes（n）	3	2		
No（n）	4	4		
Preoperative evaluation				
FEV1（%）	51.33±8.01	52.7±7.91	0.571	0.571
ppoFEV1（%）	27.65±6.99	26.84±7.01	0.384	0.703
DLCO（%）	60.65±12.07	59.38±11.8	0.353	0.726
ppoDLCO（%）	21.76±4.2	22.11±4.04	0.282	0.780
VO2max(ml/kg/min)	30.72±2.1	29.73±2.03	1.590	0.119
ppoVO2max(ml/kg/min)	50.77±7.1	51.68±6.01	0.459	0.649
VO2max(%)	8.76±1.7	9.04±1.97	0.505	0.616
ppoVO2max(%)	3.11±1.7	3.54±1.39	0.918	0.364

2.2 Training program

Seat pedal power car (Italia, COSMED Egro900) was used in loading exercise training. The intensity was among the corresponding 60-80%VO2max loading powder range of the maximum symptom-limited cardiopulmonary exercise test in the first time, which is the 20%incremental loading deviation value every two days during the practice periods. In the beginning, 1 min preheat of 15 w was conducted, and subsequently a speed of 60-70 r/min treadmill practice was conducted in the same day, and 5 min treadmill practice of 15 w was conducted during the recovery period. Electrocardiogram, blood pressure, and blood oxygen saturation were monitored during the practice periods, and proper quantity oxygen flux (2-5L/min) was provided by nasal catheter to maintain individual transcutaneous oxygen saturation (SPO2%) ≥90%. The maximum heart rate < 100% that of the predicted heart rate, and systolic pressure < 220mmHg and diastolic pressure < 110mmHg were controlled, and treadmill time was determined by the different individual tolerance degrees. Patients with hypertension were treated with antihypertensive agents to the safe range. The treadmill and the rest were conducted alternately with a time ratio of 1:1, and the daily cumulative treadmill time was 40 minutes with 5 continuous days in a week and it was lasted for 2 weeks. During each movement intermittent period, patients were guided to conduct thoracic abdominal slow pursed-lip breathing training. Briefly, patients seated and took a deep breath with the maximum inspiratory capacity by nose, and when they inhaled with chest expansion and abdominal bulge, and they held the breath for 5 seconds. When patients took breath with pursed lips, gas was exhaled slowly to the maximum expiratory volume in 4-6 seconds, with abdominal contraction and chest relaxed when they exhaled.

2.3 Effect monitoring and indicators

Static lung function was measured using the standard methods such as forced vital capacity (FVC）, FEV1, maximal voluntary ventilation (MVV), diffusion capacity for carbon monoxide of the lung (DLCO) and (DLCO/VA)[4]. Maximum symptom-limited cardiopulmonary exercise function was evaluated by treadmill experiments. Briefly, incremental exercise program was employed with resting for 1 minute, no loading exercise for 2 minutes and loading exercise with increasing 10-20 watts per minute. When a patient showed symptoms or signs of termination, load exercise was stopped [3] and numerous indices including maximal exercise load (Wmax), VO2max, anaerobic threshold (AT), oxygen pulse (VO2/HR), maximal heart rate (HRmax), maximal minute ventilation, (VEmax), respiratory index (RI), ventilatory equivalent for CO_2 (VE/VCO2@AT) and SPO2% were recorded. Changes of operation in the group B were recorded. Postoperative cardiopulmonary complications, Oxygen therapy, mechanical ventilation time and hospital days were all observed. The experiment was conducted blindly and thus physicians did not know grouping of patients.

2.4 Statistical analysis

Experiments in each group were repeated 3 times. SPSS 16.0 software was used for the analysis. Measurement data were expressed as mean ± SD ($\bar{x}$ ±s). Comparison before and after exercise training was analyzed by Student’s paired t-test using SPSS version 16.0 software. Two independent samples t-test was used and compared in the training group and the control group. χ2–test and Fisher’s exact probability calculation method were used in comparison of enumeration data between groups. A P value of less than 0.05 was considered statistically significant.

3. Results

The quality of life of the patients, changes of lung function and static lung function were all compared before and after exercise training. Table 2 demonstrated that FVC, FEV1/FVC%, MVV, DLCO, DLCO/VA, Wmax, VO2max, AT, VO2/HR, VEmax and SPO2% after exercise training all significantly increased, and RI and VE/CO2@AT significantly decreased. There was no statistical difference in respect to FEV1 and HRmax.

Table 2. Comparison of the Index of lung function and cardiopulmonary function before and after exercise training

Function Index	Before exercise training (n=39)	After exercise training (n=39)	χ^2/t	*p* value
Static lung functio				
FVC（L）	2.28±0.41	4.03±2.22	4.841	0.001
FEV1（L）	1.14±0.20	1.25±0.23	1.844	0.069
FEV1/FVC（%）	50.64±7.17	56.78±8.73	3.390	0.001
MVV（L）	50.42±9.56	56.63±9.92	2.820	0.006
DLCO	16.23±3.36	20.18±5.05	4.067	0.000
DLCO /VA	3.30±0.56	3.69±0.83	2.577	0.017
Exercise training lung function				
WRmax(Watt)	87.74±20.58	101.02±23.24	2.804	0.006
VO2max (L)	1.29±0.33	3.49±0.68	18.177	0.000
AT(ml/kg/min)	14.77±3.64	17.92±4.20	3.539	0.001
HRmax	139.84±15.01	145.77±16.57	1.656	0.102
VO2/HR(ml/bpm)	9.36±2.45	12.22±3.22	4.414	0.000
VEmax(L)	47.33±8.28	51.9±9.58	2.254	0.027
RI(%)	94.4±6.44	98.47±6.96	2.681	0.009
VE/VCO2@AT	33.0±6.00	36.73±6.32	2.673	0.009
SPO2(%)after exercise training	93.0±3.00	95.1±3.01	3.086	0.003

Operation risks were reevaluated in the no operation group B after exercise training. Results showed that 10 patients (59.0%) attained operation criterion. Compared with that of the operation group A, prevalences of the postoperative cardiopulmonary complications in the no operation group B were 40% (4/10) and 34.1% (15/44), respectively, but there was no significant difference (P=.724), See table 3. Table 4 showed that there was no statistical difference between the exercise subsection A1 and the control group A2.

Table 5 showed that there was no statistical difference in respect to the overall postoperative cardiopulmonary complications and individual prevalence between the exercise subsection A1 and the control group A2, but oxygen therapy time, mechanical ventilation time and postoperative hospital stay reduced obviously in the exercise training group.

Table 3. Status of patients received operation in the exercise operation group B

	Operation Group A	Operation Group B	χ^2	p
Reach the operation standard	-	10/17		
cardiopulmonary complication after operation	15/44	4/10	0.125	0.724

Table 4. Comparison of patients received operation in the exercise subsection A1 and the control group A2

	the exercise subsection A1	The control group A2	χ^2/t	P value
Excision ranges	19/3	17/5	0.611	0.434
Single / double lung lobe(n)				
Resection of pulmonary segments	4.27±1.08	3.91±0.99	1.153	0.256
Incision modes				
Lateral thoracic small incision (n)	12/10	10/12	0.364	0.547
Operation time (min)	228.12±88.52	208±78.11	0.799	0.429
Amount of blood loss (ml)	322.72±35.61	331±40.71	0.718	2.018

Table 5. Comparison of postoperative patients in the exercise subsection A1 and the control group A2

	The exercise group A1	The control group A2	χ^2/t	p value
Cardiopulmonary complications (n,%)	6(27.3)	9(40.9)	0.910	0.340
arrhythmia (n,%)	5(22.7)	8(36.4)	0.983	0.322
Pulmonary infection (n,%)	3(13.6)	6(27.3)	1.257	0.262
atelectasis (n,%)	4(18.2)	7(31.8)	1.091	0.296
respiratory failure (n,%)	4(18.2)	9(40.9)	2.730	0.099
postoperative death number in 30 days (n,%)	0(0%)	2(9.1%)	2.095	0.148
oxygen therapy time（hours）	73.7±28.73	105.2±62.36	2.152	0.037
mechanical ventilation time（hours）	9.6±19.72	26.2±29.86	2.176	0.036
Postoperative hospital stay	11.8±3.23	14.9±5.16	2.389	0.021

4. Discussion

Evidence-based medicine grade is A grade with lower limb movement training as the main form of submaximal exercise with moderate to severe core project of pulmonary rehabilitation in patients with COPD, which is recommended by the American College of Chest Physicians Association and the American Heart Association of pulmonary rehabilitation (ACCP/AACVPR) evidence-based medicine pulmonary rehabilitation guidelines [5]. At present, the exercise training in pulmonary rehabilitation research is mainly used to improve COPD in patients with difficult breathing, and increase exercise tolerance and quality of life [6], but researches on the preoperative exercise training in lung cancer patients with poor pulmonary function is rarely reported by foreign researchers [7].

It is hard to accept middle intensity and long cycle (4-12 weeks) exercise for those patients with lung cancer who are eager to accept operation treatment, resulting in less trainees and some trainees have difficulty in adhering to the complete training. Furthermore, effects of preoperative exercise training on pulmonary resection were rarely investigated by setting up random controls.

In order to be accepted easily by patients, short term (2 weeks) lower limb and loading exercise was employed in the present study. To receive some training effects in short term for patients, and to prevent harmful effects incurred by improper training, pedal power bicycles of individual, middle and high intensity and intermittent training method were used in the study. Although there is no unified standard on exercise training for COPD patients, it has been confirmed [8,9] that lower extremity aerobic exercise training can improve the coordinating working ability of heart and lung, and significantly improve the maximal oxygen uptake and exercise tolerance by the researches on lung recovery of COPD patients. There is relationship between strength and effect for exercise training, and relatively high intensity exercise can obtain specific physiological changes, such as increased muscle fiber capillary and mitochondrial density, increased muscle oxidase, enhanced oxygen carrying ability. However, there is no similar change in the low intensity exercise training. Compared with that of the persistent mode of exercise, intermittent training method not only significantly improves physiological indexes and exercise endurance in a same degree, but also is helpful in recovery of body energy substances such as ATP and phosphocreatine, and elimination of fatigue substances in the body by reducing accumulation of H+, and alleviating the suppression effects of acidity on phosphofructokinase, and recovery of providing ATP ability by glycolysis under low level of phosphocreatine, which is helpful in alleviating dyspnea symptoms during exercise, and is applicable to those patients with reduced exercise tolerance.

The present investigation demonstrated that all the 39 patients completed the exercise training for 2 weeks, and there was no bad reaction. Pulmonary ventilation function was improved after exercise training, and only FEV1 showed no obvious change, indicating that exercise training can not reverse airway obstructions of the middle and severe COPD patients, which is in accordance with the typical lesions of COPD, irreversible airflow restriction. Compared with that of the pre-training, other lung ventilation indices including FVC, static MVV and training VEmax all obviously increased. However, RI reduced dramatically. Under middle and high intensity training for the patients, Ventilation needs increases, which enhances deep breath and thoracoabdominal breathing is mobilized. In the meantime, respiratory muscle is exercise again during the intermittent period of training combined with pursed-lip breathing training. In addition, pulmonary ventilation function improved. Various function indices including DLCO, VE/VCO2@AT and SPO2% all improved significantly after exercise training. The reason might be that the number of opening pulmonary capillary and pulmonary blood flow increased, and pulmonary blood flow speed accelerated under the middle and high intensity conditions. Another reason might be that the jointly improved ventilation and blood flow enhanced pulmonary diffusion function and oxygen exchange ability. Moving ability and oxygen intake ability enhanced, which is characterized by dramatically enhanced Wmax, VO2max and AT. There was no obvious change in HR max enabled by the extended training time, and thus VO2/HR increased, which is the final result of the improved lung respiratory function. The enhanced pulmonary ventilation function resulted in more rapidly discharged carbon dioxide, reducing accumulation of acid productions in vivo, and alleviating fatigue feeling. The improved pulmonary ventilation function led to enhanced exchange function of oxygen, and increased tissue oxygen supply ability, and especially the improved lower limb skeletal muscle mitochondrial oxidative capacity, which extended the aerobic exercise time.

The evaluation of the recovery effects of pulmonary rehabilitation in patients with lung cancer is different from that of the single COPD patients, and it is more emphasis on whether patients can receive operation and the subsequent postoperative cardiopulmonary complications. Results showed that there were 59% patients in the no operation group B received operation because of the dramatically improved DLCO and VO2max after exercise training. Compared with that of the operation group A, there was no obvious difference in respect to prevalence of postoperative cardiopulmonary complications. The patients in the operation group A were randomly divided into the exercise group A1 and the control group A2 before exercise training in a single blind manner. There was no obvious difference in these two groups in respect to preoperative and intraoperative operations. Results demonstrated that compared with that of the control group A2, prevalences of various cardiopulmonary complications all decreased in some degree in the group A1 after pulmonary resection. The reason might be that the sample size was small, and there was no significant difference. However, oxygen therapy time, mechanical ventilation time and postoperative hospital stay time all significantly reduced, indicating that preoperation training effects were specific and persistence.

In conclusion, there are two objectives for rehabilitation therapy of the Lung cancer patients with poor pulmonary function, one of which is to improve preoperative lung function and attain operation therapy chances, and the other of which is to reduce risks of cardiopulmonary complications after pulmonary resection. Although some researches at home and abroad in recent years have confirmed that pulmonary rehabilitation in the perioperative periods including mainly chest physiotherapy and respiratory muscle training has positive significance for the lung cancer patients with pulmonary resection [10], various factors such as wound pains of the lung cancer patients with pulmonary resection and poor physical conditions often restrict pulmonary rehabilitation therapy of exercise training in the perioperative periods. Therefore, preoperative exercise training is especially important. Preoperative short-term middle and high intensity exercise training program of pedal power car in the present study can individually, quantitatively, safely and effectively enhances preoperative cardiopulmonary function adaptability of the lung cancer patients with poor pulmonary function, which is helpful for postoperative rehabilitation and is easily accepted by patients, and which thus has certain clinical application value.

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References

1. American Thoracic Society. (2003)American College of Chest Physicians : ATS/ACCP statement on cardiopulmonary exercise testing [J]. Am Respir Crit Care Med 167 (2): 211-277
2. Colice GL, Shafazand S, Griffin JP, Keenan R and Bolliger CT; American College of Chest Physicians (2007) Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2nd edition) [J]. Chest 132 (supp3):161-177
3. Caihong Zhang, Honghua Guo and Xiaoxia Cai (2012) Research progress of effects of exercise training on rehabilitation of patients with chronic obstructive pulmonary disease during stable stages [J]. CJRM 27 (5):477-480
4. Chunhui Shen and Guowei Che (2011) Application and progress of pulmonary rehabilitation in lung cancer patients during operation periods [J]. Chinese Journal of rehabilitation medicine 26(7): 686-689.
5. Jinping Zheng and Rongchang Chen (2007) Basic and clinical studies of pulmonary function. [M]. Guangdong: Guangdong science and Technology Press 34-40
6. Jones LW，Peddle CJ，Eves ND et al (2007) Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesion [J]. Cancer 110(3):590-598
7. Jing Zhang and Ruyun Yan (2010) Research progress of pulmonary rehabilitation and exercise prescription in COPD patients [J]. Chinese Journal of rehabilitation medicine 25(12):1220-1224
8. Qi Liang, Rui Jiao and Qin Jiang (2011) Effects of short term and high intensity Intermittent exercise training on Young men exercise tolerance. Chinese Journal of rehabilitation medicine 26(10): 925-928
9. Respiratory diseases, chronic obstructive pulmonary disease study group of the Chinese Medical Association. (2007) Diagnosis and treatment guidelines of the chronic obstructive pulmonary disease (The revised edition of 2007) [J]. Chinese Journal of tuberculosis and respiratory 30(1): 8-17
10. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, Make B, Rochester CL, Zuwallack R and Herrerias C (2007) Pulmonary Rehibilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines [J]. Chest 131(5 Suppl):4S-42S.

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