american physiological society®
JOURNAL OF
APPLIED PHYSIOLOGY®

J Appl Physiol 131: 1701–1707, 2021.
First published October 28, 2021; doi:10.1152/japplphysiol.00506.2021

CASE STUDIES IN PHYSIOLOGY

Case Studies in Physiology: Cardiopulmonary exercise testing and inspiratory muscle training in a 59-year-old, 4 years after an extrapleural pneumonectomy

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Abstract

This case report characterizes the physiological responses to incremental cycling and determines the effects of 12 wk of inspiratory muscle training (IMT) on respiratory muscle strength, exercise capacity, and dyspnea in a physically active 59-yr-old female, 4 years after a left-sided extrapleural pneumonectomy (EPP). On separate days, a symptom-limited incremental exercise test and a constant work rate (CWR) test at 75% of peak work rate (WR) were completed, followed by 12 wk of IMT and another CWR test. IMT consisted of two sessions of 30 repetitions twice daily for 5 days per week. Physiological and perceptual variables were measured throughout each exercise test. The participant had a total lung capacity that was 43% predicted post-EPP. A rapid and shallow breathing pattern was adopted throughout exercise, and the ratio of minute ventilation to carbon dioxide output was elevated for a given work rate. Oxygen uptake was 71% predicted and WR was 88% predicted. Following IMT, maximal inspiratory pressure improved by 36% (−27.1 cmH_2O) and endurance time by 31 s, with no observable changes in any submaximal or peak cardiorespiratory variables during exercise. The intensity and unpleasantness of dyspnea increased by 2 and 3 Borg 0–10 units, respectively, at the highest equivalent submaximal exercise time achieved on both tests. Despite having undergone a significant reduction in lung volume post-EPP, the participant achieved a relatively normal peak incremental WR, which may reflect a high level of physical conditioning. This case report also demonstrates that IMT can effectively increase respiratory muscle strength several years following EPP.

NEW & NOTEWORTHY Constraints on tidal volume expansion and the adoption of a rapid and shallow breathing pattern result in a ventilatory limitation and increased ventilatory inefficiency during exercise in a patient several years after extrapleural pneumonectomy (EPP). Inspiratory muscle training can effectively increase respiratory muscle strength after EPP.

cardiopulmonary exercise testing; dyspnea; extrapleural pneumonectomy; inspiratory muscle training; malignant pleural mesothelioma

INTRODUCTION

Malignant pleural mesothelioma is an aggressive form of cancer often associated with the exposure to asbestos. It is characterized by tumors of the mesothelium, or the surface layer of tissue lining the lungs and thoracic cavity. Extrapleural pneumonectomy (EPP) is a radical surgical option for mesothelioma, which involves the en bloc resection of the affected lung, pericardium, and ipsilateral hemidiaphragm (1). In addition, patients often undergo chemotherapy and radiation, which are not always used in conjunction with pneumonectomy, and further negatively affect an individual's functional capacity (2). Functional capacity can be evaluated with cardiopulmonary exercise testing (CPET), which provides an in-depth assessment of the integrated physiological responses to exercise, as well as the impacts and/or benefits from treatments. To our knowledge, CPET has not been reported in an individual several years after an EPP.

Respiratory muscle strength and exercise capacity are significantly reduced with the removal of the affected lung (3, 4). One study found maximal inspiratory pressure (MIP) to be 50% and 15% of preoperative values 1 and 12 wk after lung resection, respectively (3). Therefore, inspiratory muscle training (IMT) in patients post-EPP may have the potential to improve exercise tolerance as has been shown in healthy

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Submitted 14 July 2021 / Revised 15 October 2021 / Accepted 20 October 2021

individuals, as well as those with chronic obstructive pulmonary disease (5, 6), among others. However, to our knowledge, there are no reports of IMT following EPP. Therefore, the purpose of this case study was to characterize the physiological responses to CPET and evaluate the impact of IMT on MIP, endurance time, and the multidimensional evaluation of dyspnea in an individual after an EPP.

MATERIALS AND METHODS

The Participant

The participant was a 59-yr-old female who underwent an EPP with preoperative radiation 4 years before this study (Fig. 1). The EPP involved the removal of the left lung, resection of the left phrenic nerve, and resection and reconstruction of the pericardium and left hemidiaphragm with Gore-Tex mesh. The sixth rib was partially removed and incisions were made into the fifth and sixth intercostal muscles, which were sutured back together. A small portion of the left main bronchus remained post-EPP via bronchoscopy. This normotensive participant was not taking any medications throughout the study and is an avid tennis player who wished to improve her exercise capacity via IMT. The participant gave written informed consent and the experimental procedures received institutional ethical approval (H18-02509).

Experimental Overview

The participant visited the laboratory for three experimental visits and once weekly during a 12-wk IMT program. The participant was asked to avoid caffeine and strenuous physical activity before each experimental visit. The first visit included anthropometric measurements; a detailed medical history; health-related questionnaires; and a symptom-limited incremental cycling CPET. The second and third visits were completed before and after IMT and involved constant work rate (CWR) cycling tests.

Exercise Protocol

All exercise tests were conducted on an electronically braked cycle ergometer (VIAsprint 200 P; Ergoline, Bitz, Germany). The incremental test started at 20 W and increased by 20 W every 2 min in a stepwise fashion until symptom limitation. The CWR tests were performed at 75% of the peak incremental work rate (WR) until symptom limitation.

Inspiratory Muscle Training

IMT was performed using a POWERbreathe K3 5 days per week, twice per day (morning and evening), with each session consisting of two sets of 30 inspirations with 2 min of rest between sets. The participant was instructed to inhale as strongly and deeply as possible and exhale as slowly and deeply as possible. The first session of each week was conducted at the laboratory to ensure proper technique and to set the training intensity. The IMT program began at an initial training intensity corresponding to 50% of the average presession MIP, based on previous work in our laboratory (7) and others (6). Each week the target intensity was adjusted to maintain at least 50% of the average presession MIP or such that the participant was training at a 30-repetition maximum intensity, whichever was greater.

Anthropometric Measurements and Pulmonary Function

Height and mass were measured (Seca 769; Seca, Chino, CA) followed by spirometry, plethysmography, and maximal respiratory pressures (Vmax 229d with Autobox 6,200 DL; SensorMedics, Yorba Linda, CA) (8, 9) with measurements expressed as absolute values and as percentages of predicted where appropriate (10–13).

Cardiorespiratory and Metabolic Parameters

Standard cardiorespiratory measures were recorded and averaged over 30 s epochs using a metabolic cart (TrueOne 2400; Parvo Medics, UT) during all exercise tests. Operating volumes were derived from dynamic inspiratory capacity (IC) maneuvers (14). The presence or absence of expiratory flow limitation (EFL) was determined by placing expiratory tidal flow-volume curves within the maximum expiratory flow-volume curve as described previously (15). Heart rate (HR) and peripheral oxygen saturation were measured using a

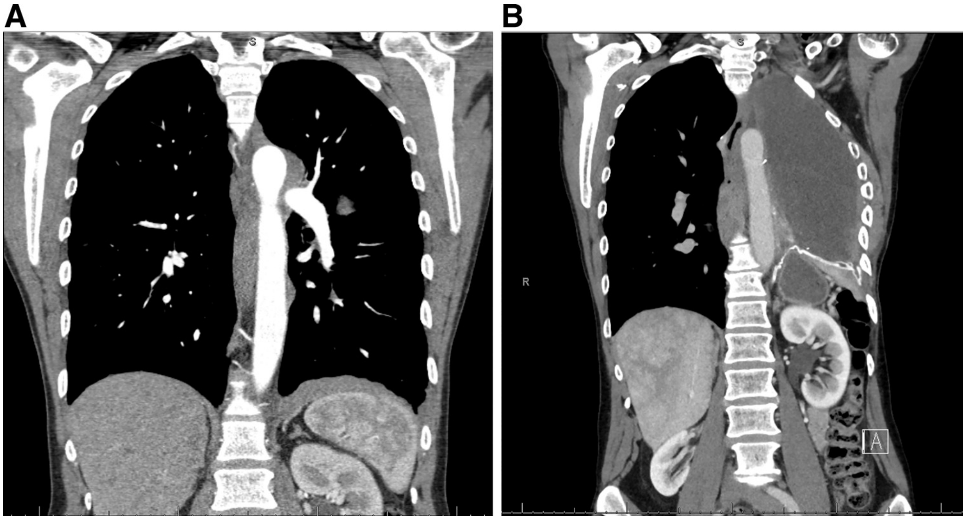

Figure 1. Computed tomography (CT) scans pre-EPP (*left*) and post-EPP (*right*). EPP, extrapleural pneumonectomy.

telemetric sensor and pulse oximetry, respectively. Select cardiorespiratory and metabolic variables were expressed as a percentage of predicted values (16).

Symptom Evaluation

The participant was asked to rate her perception of dyspnea intensity, dyspnea unpleasantness, and leg discomfort using the modified Borg 0–10 category ratio scale (17) at rest and during each 2-min stage of exercise using the following questions: "How intense is your sensation of breathing overall?", "How unpleasant or badly does your breathing make you feel?", and "What is your overall sensation of leg discomfort?" A script was read on all experimental visits for standardization and to help the participant distinguish between breathing intensity and unpleasantness. The multidimensional dyspnea profile (MDP) was also administered at peak exercise (18).

RESULTS

Physiological Responses to Incremental Cycling Exercise

Anthropometric characteristics and peak incremental exercise data are shown in Table 1. The participant self-reported over five times the recommended metabolic equivalents per week of physical activity (19). Physiological responses to incremental cycling are shown in Fig. 2, along with data from a group of healthy physically active female controls (n = 9) of similar age and body mass index from our laboratory (20). Peak WR and O_2 uptake ($\dot{V}O_2$) were 88% predicted and 71% predicted, respectively. The slope of the relationship between the participant's $\dot{V}O_2$ and WR was 7.2 $mL \cdot min^{-1} \cdot W^{-1}$. Peak HR and oxygen pulse were 80% predicted and 95% predicted, respectively. Tidal volume (V_T) plateaued early and remained constrained throughout exercise. Peak minute ventilation ($\dot{V}E$) reached 88% of the measured maximal voluntary ventilation. The participant showed evidence of EFL during the last two stages of exercise (Fig. 2G). The ventilatory equivalent for CO_2 ($\dot{V}E/\dot{V}CO_2$) was elevated at the gas exchange threshold (21). There was no evidence of exertional hypoxemia.

Table 1. *Baseline characteristics and peak exercise data*

	EPP	Control
Anthropometric characteristics		
Age, yr	59	65 ± 5
Height, cm	166	165 ± 6
Mass, kg	55.9	61 ± 7
Body mass index, $kg \cdot m^{-2}$	20.4	22.4 ± 2.2
Peak exercise		
Work rate, W	100	129 ± 27
$\dot{V}O_2$, $L \cdot min^{-1}$	1.07	1.62 ± 0.29
$\dot{V}O_2$, $mL \cdot kg^{-1} \cdot min^{-1}$	19.1	26.8 ± 4.00
$\dot{V}CO_2$, $L \cdot min^{-1}$	1.15	1.76 ± 0.25
Respiratory exchange ratio	1.07	1.09 ± 0.07
$\dot{V}E$, $L \cdot min^{-1}$	46.2	62.3 ± 12.4
V_T, L	0.84	1.69 ± 0.28
V_T/forced vital capacity, %	53	48 ± 3
Breathing frequency, $breaths \cdot min^{-1}$	55	37 ± 5
$\dot{V}E/\dot{V}O_2$	43	39 ± 8
$\dot{V}E/\dot{V}CO_2$	40	35 ± 5
$\dot{V}E$/maximal voluntary ventilation, %	88	61 ± 14
Heart rate, $beats \cdot min^{-1}$	122	156 ± 16
Oxygen pulse, mL/beat	8.8	10.6 ± 2.4
Breathing intensity, scale = 0–10	4	6 ± 1
Breathing unpleasantness, scale = 0–10	5	NA
Leg discomfort, scale = 0–10	4	7 ± 2

EPP, extrapleural pneumonectomy; NA, not applicable; $\dot{V}CO_2$, CO_2 output; $\dot{V}E$, minute ventilation; $\dot{V}O_2$, O_2 uptake; V_T, tidal volume.

Effects of IMT

Following IMT, the participant's MIP increased by 36% (pre-IMT = −75.3 cmH_2O vs. post-IMT = −102.4 cmH_2O). The participant's pulmonary function, questionnaire data, and physiological and sensory responses to CWR exercise pre-IMT and post-IMT are shown in Table 2. There were no observable differences in any submaximal or peak cardiorespiratory or metabolic variables during the CWR tests. Dyspnea intensity, dyspnea unpleasantness, and leg discomfort ratings were all 0 units at baseline. From rest, the participant rated all three symptoms 3 units higher during the first 2-min of exercise post-IMT and consistently rated dyspnea intensity 2–3 units higher for the remainder of the post-IMT exercise test. At the highest equivalent submaximal exercise time (HESET) achieved on both tests, dyspnea intensity, dyspnea unpleasantness, and leg discomfort increased by 2, 3, and 3 units, respectively. Breathing unpleasantness at peak exercise increased from 7 to 9 units post-IMT using the MDP. All sensory qualities of the MDP at peak exercise increased by 1–3 units post-IMT, except for the phrase "my chest and lungs feel tight or constricted," which remained the same (7 units). The affective dimension of frustration increased from 7 to 9 units pre-IMT to post-IMT and an intensity of 1 unit was attributed to anger and anxiety post-IMT only.

DISCUSSION

This case study characterizes the physiological responses to maximal incremental cycling, as well as the effects of IMT on MIP, endurance time, and dyspnea ratings in a 59-yr-old physically active female, 4 years after a left-sided EPP. The main findings of this case study include *1*) evidence of mechanical ventilatory constraint during exercise and a small ventilatory reserve at peak exercise; *2*) ventilatory inefficiency, as demonstrated by an elevated $\dot{V}E/\dot{V}CO_2$; *3*) a 36% increase in MIP pre-IMT versus post-IMT; *4*) a 31 s increase in CWR endurance time post-IMT; *5*) higher ratings of dyspnea intensity and unpleasantness at the HESET post-IMT; and *6*) a higher intensity of frustration, anger, and anxiety at peak exercise post-IMT.

Physiological Responses to Incremental Cycling Exercise

CPET provides a measurement of the integrated responses of the respiratory, cardiovascular, muscular, and other physiological systems to determine the factors that contribute to a low peak $\dot{V}O_2$. In the present study, the participant reached a peak $\dot{V}O_2$ that was 71% predicted (Fig. 2A), which is similar to a previous study of patients post-pneumonectomy whose peak $\dot{V}O_2$ was ~65% predicted 6 mo postoperatively (22). The slope of the relationship between $\dot{V}O_2$ and WR was surprisingly low, which may be explained by the reduction in pulmonary surface area post-EPP, which attenuated the exchange of $\dot{V}O_2$ and $\dot{V}CO_2$ at the lung and negatively influenced O_2 delivery rather than impairing O_2 extraction at the level of the peripheral muscles. The low-peak $\dot{V}O_2$ following EPP may be explained, at least in part, by an abnormal ventilatory response to exercise. For example, V_T plateaued early and remained constrained throughout exercise, resulting in

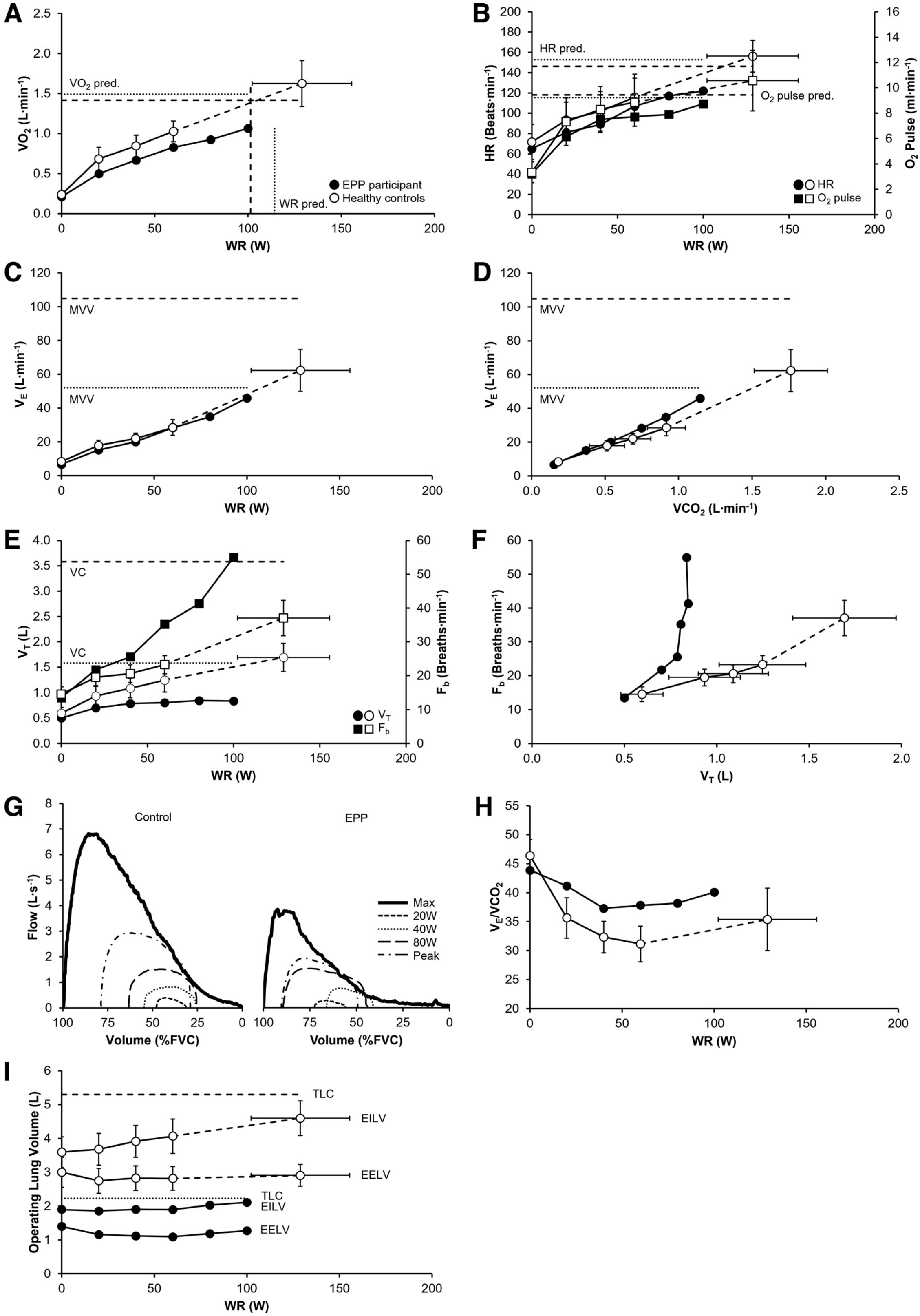

Table 2. *Pulmonary function, questionnaires, and constant work rate data at symptom limitation*

	Pre-IMT	Post-IMT
Pulmonary function		
FVC, L	1.58 (46)	1.63 (48)
FEV_1, L	1.16 (45)	1.06 (41)
FEV_1/FVC, %	73 (97)	65 (87)
FRC, L	1.26 (43)	1.45 (49)
RV, L	0.65 (35)	0.87 (46)
IC, L	0.97 (37)	1.08 (41)
VC, L	1.58 (46)	1.66 (48)
TLC, L	2.23 (43)	2.53 (48)
MVV, $L \cdot min^{-1}$	52 (111)	56 (120)
Questionnaires		
IPAQ-LF, $MET \cdot min^{-1} \cdot wk^{-1}$	2,520	2,892
UCSD SOBQ (0–100)	0	25
SGRQ (0–100)	21.0	26.2
Constant work rate exercise		
Work rate, W	75	75
Endurance time, s	571	602
$\dot{V}O_2$, $L \cdot min^{-1}$	1.04	1.01
$\dot{V}O_2$, $mL \cdot kg^{-1} \cdot min^{-1}$	18.7	18.2
$\dot{V}CO_2$, $L \cdot min^{-1}$	1.07	1.08
Respiratory exchange ratio	1.03	1.07
$\dot{V}E$, $L \cdot min^{-1}$	43.0	45.9
V_T, L	0.86	0.85
Breathing frequency, $breaths \cdot min^{-1}$	50	54
$\dot{V}E/\dot{V}O_2$	41	45
$\dot{V}E/\dot{V}CO_2$	40	43
EELV, l (%TLC)	1.17 (53)	1.50 (59)
EILV, l (%TLC)	2.03 (91)	2.31 (91)
Heart rate, $beats \cdot min^{-1}$	125	126
Oxygen pulse, $mL \cdot beat^{-1}$	8.3	8.0
$\dot{V}E$/MVV, %	83	82
Breathing intensity, scale = 0–10	7	9
Breathing unpleasantness, scale = 0–10	5	9
Leg discomfort, scale = 0–10	5	9
Breathing unpleasantness, 0–10 MDP	7	9
Depressed, 0–10 MDP	0	0
Anxious, 0–10 MDP	0	1
Frustrated, 0–10 MDP	7	9
Angry, 0–10 MDP	0	1
Afraid, 0–10 MDP	0	0

Values in parentheses are % predicted values unless otherwise stated. EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; IMT, inspiratory muscle training; IPAQ-LF, International Physical Activity Questionnaire-Long Form; MDP, multidimensional dyspnea profile; MVV, maximum voluntary ventilation; RV, residual volume; SGRQ, St. George's Respiratory Questionnaire; TLC, total lung capacity; UCSD SOBQ, The University of California-San Diego Shortness of Breath Questionnaire; VC, vital capacity; $\dot{V}CO_2$, CO_2 output; $\dot{V}E$, minute ventilation; $\dot{V}O_2$, O_2 uptake; V_T, tidal volume.

a rapid and shallow breathing pattern. Moreover, physiological dead space was likely elevated by the removal of one lung (23), especially since a portion of the left main bronchus remained post-EPP. This is supported by the higher $\dot{V}E/\dot{V}CO_2$ for a given WR in our study participant compared with healthy controls (Fig. 2*H*). Ventilatory inefficiency can also be explained by the reduction in pulmonary surface area post-EPP, which required a greater $\dot{V}E$ for a given $\dot{V}O_2$ or $\dot{V}CO_2$ than healthy controls. Interestingly, $\dot{V}E$ for a given WR in our study participant was nearly identical to healthy controls, despite representing a greater fraction of ventilatory capacity. Ventilatory reserve was less than 15% at peak exercise and there was evidence of EFL near-maximal exercise (Fig. 2, *C* and *G*, respectively). Despite evidence of ventilatory constraint, peripheral oxygen saturation remained at resting levels (96%) throughout exercise. The maintenance of oxygen saturation may be explained by an improvement in the relationship between $\dot{V}E$ and perfusion as the full systemic circulation is directed through the remaining lung post surgery (24).

A low peak $\dot{V}O_2$ can also be explained by a cardiovascular limitation to exercise. Multiple studies in patients post-pneumonectomy have reported a low cardiac output during exercise, primarily due to a reduction in stroke volume (25, 26). In the present study, the participant achieved a maximal HR and oxygen pulse (index of stroke volume) of 80% predicted and 95% predicted, respectively (Fig. 2*B*). There was a HR reserve of 31 $beats \cdot min^{-1}$ in the absence of a plateau in either HR or oxygen pulse, which suggests that cardiac function likely did not contribute to exercise intolerance. The discrepancy with previous studies in patients post-pneumonectomy is unknown. However, it should be noted that our participant did not show signs of mediastinal shift and the left chest wall was contracting inward (i.e., left-sided ribs are closer to the midline than the right-sided ribs; Fig. 1), which differs from the typical patient post-pneumonectomy. The different morphological presentation in our participant likely limits lung expansion, but may improve stroke volume compared with other patients post-pneumonectomy; however, this remains speculative.

Effects of IMT

In the present report, the participant improved MIP by 36% over 12 wk of IMT, which is greater than the 14% improvement in MIP following IMT in patients after lung resection (27). The discrepancy may be due, at least in part, to the duration of time since surgery. Most postoperative IMT studies occur for 2–12 wk within the first few days or weeks post surgery. It is likely that these patients are still recovering from the procedure. In addition, some patients report pain while performing MIP maneuvers within the first few weeks after surgery (28).

CWR endurance time was improved by 31 s despite no observable differences in submaximal or peak physiological variables post-IMT (Table 2). It is possible that the modest

Figure 2. CPET responses (black symbols and dotted lines) vs. nine healthy female controls of similar age and body mass index (white symbols and dashed lines) (age = 65 ± 5 yr, height = 165 ± 6 cm, mass = 61 ± 7 kg). *A–I*: shows the relationship between $\dot{V}O_2$ and WR (*A*), cardiac responses (*B*), the ventilatory response (*C*), the relationship between $\dot{V}E$ and $\dot{V}CO_2$ (*D*), breathing patterns (*E* and *F*), expiratory flow limitation via maximal flow-volume curve (solid black line), and tidal exercise flow-volume curves at baseline, 40 W, 80 W, and peak exercise (dashed lines) (*G*), the ventilatory equivalent for CO_2 (*H*), and operating lung volumes during exercise (*I*). CPET, cardiopulmonary exercise testing; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; F_b, breathing frequency; FVC, forced vital capacity; HR, heart rate; MVV, maximum voluntary ventilation; O_2, oxygen; TLC, total lung capacity; VC, vital capacity; $\dot{V}CO_2$, carbon dioxide output; $\dot{V}E$, ventilation; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $\dot{V}O_2$, oxygen uptake; V_T, tidal volume; WR, work rate. Data are presented as means ± standard deviation for the control group. Reproduced and modified from Ref. 31.

improvement in endurance time may be explained by learning and/or placebo effects or it could simply reflect day-to-day variability in exercise responses. The present study did not include a familiarization test, which is a limitation of this case report; however, CWR exercise tests have been shown to be reproducible without a familiarization visit in nonathletic populations that are naïve to CWR exercise testing protocols (29). Previous studies investigating the effects of IMT on exercise capacity following lung resection are conflicting. For example, one study found no significant effect of IMT on $\dot{V}O_2$ in patients post-pneumonectomy (23), whereas another found improvements in both peak $\dot{V}O_2$ and $\dot{V}E$ but not WR when IMT was combined with aerobic exercise training in patients 6–8 wk following lung resection (30). Although our participant self-reported more physical activity post-IMT, a structured aerobic training program was not completed and thus may provide a reason for the lack of improvement in cardiorespiratory and metabolic variables in the current study. Future work combining IMT and aerobic exercise training should be investigated in patients fully recovered from EPP.

Despite an improvement in MIP in our participant, ratings of dyspnea intensity and unpleasantness increased. Moreover, the degree of dyspnea-related frustration, anger, and anxiety increased at peak exercise post-IMT. Previous work in patients post-pneumonectomy revealed that dyspnea intensity was lower but not significantly different after 4 wk of IMT (23), whereas no difference in dyspnea intensity was shown between IMT and control groups after a 6-min walk test following 2 wk of IMT in patients after lung resection (28). The reasons for the relatively large increases in dyspnea intensity and unpleasantness post-IMT in the present study are unknown. However, discussions with the participant suggest that increases in the affective responses of frustration, as well as anger and anxiety following IMT, may have reflected her disappointment in the lack of perceived improvements in exercise capacity and symptoms post-IMT. Despite her high degree of motivation and effort during the IMT program, her expectations were not met, which may have influenced her sensory responses to exercise. Interestingly, the participant did notice improvements in her ability to carry a conversation and vocalize across the tennis court, which she was unable to do before the study. Whether the improvement in her ability to communicate during physical activity without becoming short of breath was due to IMT is unknown.

Conclusions

This case report of a 59-yr-old female, 4 years after an EPP demonstrates that there were mechanical constraints on $\dot{V}E$ during exercise. Specifically, V_T plateaued early and remained constrained throughout incremental exercise, which resulted in the adoption of a rapid and shallow breathing pattern. The ability of the participant to achieve a relatively normal peak incremental WR despite her ventilatory limitation likely reflects a high level of physical conditioning and emphasizes the importance of maintaining a physically active lifestyle post-EPP. This case report also shows that IMT effectively increased respiratory muscle strength in our participant several years after an EPP. Future studies are needed with larger sample sizes to understand the effects of IMT on exercise capacity, dyspnea, and cardiorespiratory physiology following this surgical procedure.

ACKNOWLEDGMENTS

We sincerely thank the participant for approaching us and agreeing to complete this study.

GRANTS

This work was supported by a Discovery Grant from the Natural Sciences and Engineering Research Council (NSERC) of Canada. R.A.M. was supported by a Postgraduate Scholarship from the NSERC and a University of British Columbia 4-yr fellowship. A.H.R. was supported by a Canada Graduate Scholarship from the NSERC. J.A.G. was supported by a Scholar Award from the Michael Smith Foundation for Health Research and a Clinical Rehabilitation New Investigator Award from the Canadian Institutes of Health Research.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

R.A.M., S.T.A., and J.A.G. conceived and designed research; R.A.M., S.T.A., S.S.D., J.Z., K.G.B., and A.H.R. performed experiments; R.A.M. analyzed data; R.A.M., S.T.A., A.H.R., M.R.S., K.M.M., Y.M.-S., A.W.S., and J.A.G. interpreted results of experiments; R.A.M. prepared figures; R.A.M. drafted manuscript; R.A.M., S.T.A., S.S.D., J.Z., K.G.B., A.H.R., M.R.S., K.M.M., Y.M.-S., A.W.S., and J.A.G. edited and revised manuscript; R.A.M., S.T.A., S.S.D., J.Z., K.G.B., A.H.R., M.R.S., K.M.M., Y.M.-S., A.W.S., and J.A.G. approved final version of manuscript.

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