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The Association Between Preoperative Inspiratory Muscle Training Variables and Postoperative Pulmonary Complications in Subjects With Esophageal Cancer

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BACKGROUND: Preoperative inspiratory muscle training (IMT) is frequently used in patients waiting for major surgery to improve respiratory muscle function and to reduce the risk of postoperative pulmonary complications (PPCs). Currently, the mechanism of action of IMT in reducing PPCs is still unclear. Therefore, we investigated the associations between preoperative IMT variables and the occurrence of PPCs in patients with esophageal cancer. METHODS: A multi-center cohort study was conducted in subjects scheduled for esophagectomy, who followed IMT as part of a prehabilitation program. IMT variables included maximum inspiratory pressure (P_{Imax}) before and after IMT and IMT intensity variables including training load, frequency, and duration. Associations between P_{Imax} and IMT intensity variables and PPCs were analyzed using independent samples *t* tests and logistic regression analyses, corrected for age and pulmonary comorbidities and stratified for the occurrence of anastomotic leakages. RESULTS: Eighty-seven subjects were included (69 males; mean age 66.7 ± 7.3 y). A higher P_{Imax} (odds ratio 1.016, *P* = .07) or increase in P_{Imax} during IMT (odds ratio 1.020, *P* = .066) was not associated with a reduced risk of PPCs after esophagectomy. Intensity variables of IMT were also not associated (*P* ranging from .16 to .95) with PPCs after esophagectomy. Analyses stratified for the occurrence of anastomotic leakages showed no associations between IMT variables and PPCs. CONCLUSIONS: This study shows that an improvement in preoperative inspiratory muscle strength during IMT and training intensity of IMT were not associated with a reduced risk on PPCs after esophagectomy. Further research is needed to investigate other possible factors explaining the mechanism of action of preoperative IMT in patients undergoing major surgery, such as the awareness of patients related to respiratory muscle function and a diaphragmatic breathing pattern.
Key words: inspiratory muscle training; postoperative pulmonary complications; cancer; surgery; physiotherapy; respiratory muscles. [Respir Care 0;0(0):1–●. © 2023 Daedalus Enterprises]

Introduction

Despite advances in perioperative care in the last decades, the risk of postoperative pulmonary complications (PPCs) after a major thoracic or abdominal surgery remains high.[1-3] The development of PPCs seems to be related to a dysfunction of the diaphragm, the most important muscle used in inspiration, leading to a decreased inspiratory capacity after surgery.[4,5] Preoperative inspiratory muscle training (IMT), aimed at improving inspiratory muscle strength and endurance, can lead to an increase of the inspiratory capacity and a better-quality deep breathing after surgery.[6,7] Therefore, preoperative IMT can be used to reduce the risk of PPCs after a major surgery.[8,9] In patients undergoing cardiac and upper abdominal surgery, preoperative IMT has been shown to reduce the incidence of PPCs.[4,7,9-12] In patients undergoing esophagectomy, PPCs are very common (27–57%).[13-17] However, the effectiveness of IMT to reduce PPCs in patients undergoing esophagectomy varies between studies.[18-20]

Based on the current evidence, IMT seems to result in significantly improved inspiratory muscle strength after training.[10,18-20] Nevertheless, in previous studies, no clear association between an improvement of the inspiratory muscle strength and a reduced risk of PPCs after esophagectomy has been demonstrated.[18-22] Therefore, the possible mechanism of action of IMT in reducing PPCs after esophagectomy is still unclear.

An improvement of the inspiratory muscle strength and the effectiveness of IMT may also be related to the training intensity of the performed IMT. Previous studies indicate that a higher training intensity and an increase in training intensity during IMT seem to be associated with a reduced risk of PPCs.[18,20] There is no information available on the influence of the training frequency and duration of IMT on the risk of PPCs. To create more insight into the possible mechanism of action of IMT, the associations between inspiratory muscle strength and training intensity and the risk of PPCs need to be investigated further. Therefore, the aim of this study was to determine associations between preoperative maximum inspiratory pressure (P_{Imax}) and intensity variables of preoperative IMT with the occurrence of PPCs in subjects undergoing esophagectomy.

QUICK LOOK

Current knowledge

Preoperative inspiratory muscle training (IMT) seems to reduce the risk of postoperative pulmonary complications (PPCs) after major surgery. However, in previous studies, no clear associations have been demonstrated between an improvement of the inspiratory muscle strength, training intensity of IMT, and a reduction of the risk of PPCs in patients with esophageal cancer.

What this paper contributes to our knowledge

This study shows that a higher inspiratory muscle strength or increase of inspiratory muscle strength was not associated with a reduced risk of PPCs in subjects after esophagectomy. Training intensity of IMT was also not associated with the risk of PPCs after esophagectomy. These findings address the need to a better understanding and possibly to an alternative rationale for IMT before a major surgery.

Methods

Study Design

Current analyses were part of the preoperative intervention to improve outcomes in esophageal cancer patients after resection (PRIOR) study, a multi-center, observational cohort study evaluating the implementation of prehabilitation to improve (inspiratory) muscle function, general fitness, and nutritional status for patients with esophageal cancer.

Participants and Procedures

Patients in the University Medical Center Utrecht, University Medical Center Groningen, University Medical Center Utrecht, University Medical Center Groningen, Gelre Hospital, Isala Hospital, and Twente Hospital Group were asked to participate in the PRIOR study from March 2018–January 2020. The inclusion criteria were (1) diagnosis of esophageal cancer and (2) scheduled for curative treatment consisting of neoadjuvant chemoradiotherapy and esophagectomy. There were no exclusion criteria. Subjects followed a prehabilitation program consisting of physical training and nutritional support as part of the standard curative treatment pathway. Curative treatment started with a 5-week schedule of chemoradiotherapy. After completing chemoradiotherapy, subjects followed a 6–8 week training program consisting of overall physical training and IMT under the supervision of a physiotherapist, combined with nutritional support by a dietitian. After diagnosis and before the start of the medical treatment, subjects were informed about the study and asked to participate by the physiotherapist. All subjects enrolled in the study signed an informed consent for the use of their treatment data for research. This study protocol was approved by the medical ethics committee of the University Medical Center Utrecht (protocol number 17–533/C).

Inspiratory Muscle Training

IMT was performed using an inspiratory threshold-loading POWERbreathe Medic Plus device (POWERbreathe, Southam, United Kingdom). The starting level of the training sessions was based on the P_{Imax} at baseline. The resistance on the threshold ranged from 0–10, corresponding to 9–78 cm H_2O (Figure S1; see related supplementary materials at http://www.rcjournal.com). The training consisted of high-load training starting with 60% of the P_{Imax} in the first week and 80% of the P_{Imax} from the second week.

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Perceived exertion was rated using a Borg scale from 0 (no exertion) to 10 (maximal exertion). If the Borg scale was < 5, resistance was increased by 5% of the measured P_{Imax}. Six series of 6 repetitions were performed per training session. When subjects reached the maximum resistance of 78 cm H_2O, the number of repetitions per series was increased until an exertion of 5 on the Borg scale was achieved. Between each series, a resting period was scheduled. The first resting period was 60 s, and it was shortened to, respectively, 45, 30, 15, and 5 s after each subsequent series. Subjects performed the training twice a week under supervision of a physiotherapist and once a week independently at home. After each training session, the training load of the threshold trainer and the Borg score were recorded in a training log by the physiotherapist or the subject. The mean Borg score of all training sessions within a subject was calculated representing the average exertion of the subject.

Measurements

The P_{Imax} was measured with the respiratory pressure meter (Micro Medical RPM, PT Medical, Leek, the Netherlands)[23] before and after the training period. Measurements were performed on a chair without armrests, with the subject holding the mouth pressure gauge in one hand and the other arm hanging next to the body or lying loose on the leg.[24] A nose clip was placed on the subject's nose, and after a maximum exhalation, the subject closed their lips tightly around the mouthpiece of the mouth pressure gauge. The subject inhaled as forcefully as possible for a minimum of 2 s and was encouraged by the physiotherapist. The test was repeated at least 5 times with a pause of at least half a minute. The highest measured negative pressure in cm H_2O was noted. The test-retest reliability of the P_{Imax} in healthy subjects showed high reliability with an intraclass correlation coefficient of 0.78–0.87[25] and a high reliability (r = 0.97) in subjects with COPD.[26]

Intensity variables of the IMT included training load (from the first and last session, progress in training load, and mean training load), training frequency, and training duration. To determine the training load of each training session, the recorded resistance on the device was converted to the corresponding training load in cm H_2O (Figure S1 of online supplement, see related supplementary materials at http://www.rcjournal.com). The training load from each training session was also calculated as percentage of the P_{Imax} at baseline, and the mean training load in cm H_2O of all training sessions within a subject was calculated. Progress in training load was calculated by subtracting the training load of the first IMT session from the last IMT session. The mean training frequency per week was calculated by dividing the total number of IMT sessions by the number of training weeks. Training duration included the total training period in weeks.

Data on postoperative complications were obtained from the Dutch Upper Gastrointestinal Cancer Audit,[27] including the occurrence of anastomotic leakage and PPCs. PPCs included pneumonia (diagnosed in the presence of new lung infiltrate, based on imaging, plus at least 2 of the 3 clinical signs: [1] fever, [2] purulent sputum, and [3] leukocytosis or leukopenia),[28] pleural effusion requiring drainage, pneumothorax requiring treatment, mucus plug atelectasis requiring bronchoscopy, respiratory failure requiring re-intubation, acute aspiration, ARDS, and/or persistent air leakage requiring chest drainage.[29] At the presence of one of these complications, a PPC was registered. The outcome measure in this study was the occurrence of PPCs (yes/no).

Demographic and medical data were collected from the medical record and included sex, age, body mass index (BMI), pulmonary comorbidity, tumor location, tumor type, surgery procedure, and the American Society of Anesthesiologists physical status classification level.

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics version 26 (IBM, Armonk, New York). Descriptive statistics were performed on the demographic and medical data. A histogram, Q-Q plot, and Shapiro-Wilk test were used to check whether demographic and medical data were normally distributed.[30] In case of normal distribution, variables were described as mean and SD and in case of a skewed distribution as median and interquartile range. The independent sample *t* test (in case of normal distribution), Mann-Whitney U test (in case of non-normal distribution), or chi-square test was used to determine differences between subjects with and without PPCs in demographic and medical data and in P_{Imax} (at baseline, follow-up, and change in P_{Imax} between baseline and follow-up) and IMT intensity variables. To determine progression during the IMT, a paired-sample *t* test or Wilcoxon signed-rank test was used to test differences within the groups between P_{Imax} and training load at baseline and at the last training session.

Logistic regression analyses were used to assess the association of P_{Imax} and IMT intensity variables with the occurrence of PPCs, corrected for age and pulmonary comorbidities.[31,32] To investigate a possible interaction of the occurrence of anastomotic leakage on the association between P_{Imax} and IMT variables with PPCs, analyses were stratified for subjects with and without an anastomotic leakage. Odds ratios and 95% CIs were determined. The analyses were considered statistically significant if the *P* value was < .05.

Results

Between March 2018–December 2020, 248 subjects were enrolled in the PRIOR study. Of these subjects, 102 dropped out because they did not undergo surgery, measurements were stopped, subjects did not perform the IMT, or other reasons (Fig. 1). In addition, 59 subjects did not

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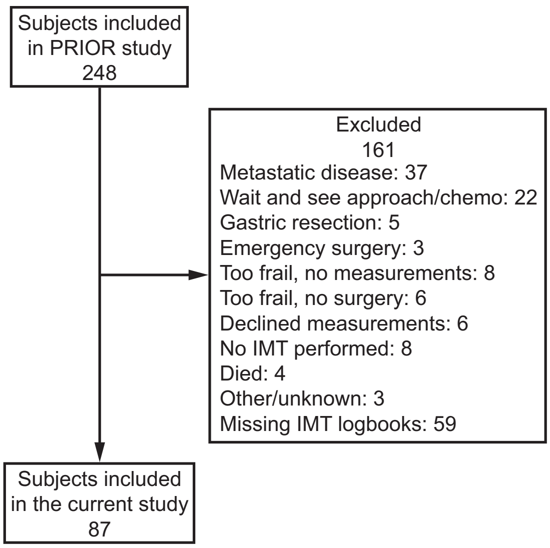

Fig. 1. Flow chart. PRIOR = preoperative intervention to improve outcomes in esophageal cancer patients after resection; IMT = inspiratory muscle training.

return an IMT log. Therefore, data from 87 subjects were analyzed, of which 69 (79.3%) were males and 18 (20.7%) females (Table 1). The mean age was 66.7 (SD 7.3) y, and the mean BMI was 26.1 (SD 3.7). PPCs were diagnosed in 29 (33.3%) of 87 subjects (Table 2). None of the demographic and medical data were significantly ($P < .05$) different between subjects with PPCs and subjects without PPCs. Demographic and medical data are presented in Table 1.

Table 1. Baseline Demographic and Medical Characteristics of Subjects

	All (N = 87)	No PPCs n = 58	PPCs n = 29	P
Sex				
Male	69 (79.3)	43 (74.1)	26 (89.7)	.09
Female	18 (20.7)	15 (25.9)	3 (10.3)	
Age, y				
Total	66.7 (7.3)	67.1 (6.9)	66.2 (8.3)	.60
Age, y				
< 60	14 (16.1)	8 (13.8)	6 (20.7)	.92
60–69	38 (43.7)	27 (46.6)	11 (37.9)	
70–79	35 (40.2)	23 (39.7)	12 (41.4)	
BMI, kg/m^2				
Total	26.1 (3.7)	25.9 (3.8)	26.4 (3.5)	.53
Comorbidity				
Pulmonary comorbidity	19 (21.8)	11 (19.0)	8 (27.6)	.36
Tumor location				
Intrathoracic, middle part	10 (11.5)	7 (12.1)	3 (10.3)	.51
Intrathoracic, distal part	72 (82.8)	47 (81.0)	25 (86.2)	
Esophagus-stomach transition	5 (5.7)	4 (6.9)	1 (3.4)	
Tumor type				
Adenocarcinoma	76 (87.4)	49 (84.5)	27 (93.1)	.25
Squamous cell carcinoma	11 (12.6)	9 (15.5)	2 (6.9)	
Surgery procedure				
Transhiatal	3 (3.4)	2 (3.1)	1 (4.5)	> .99
Transthoracic	84 (96.6)	63 (96.9)	21 (95.5)	
ASA physical status				
Normal healthy patient	4 (4.6)	2 (3.4)	2 (6.9)	.78
Mild systemic disease	51 (58.6)	33 (56.9)	18 (62.1)	
Severe systemic disease	30 (34.5)	21 (36.2)	9 (31.0)	
Constant life-threatening illness	1 (1.1)	1 (1.7)		
Unknown	1 (1.1)	1 (1.7)		
Anastomotic leakage	16 (18.4)	9 (15.5)	7 (24.1)	.33

Data are presented as n (%) or mean (SD).
PPCs = postoperative pulmonary complications
BMI = body mass index
ASA = American Society of Anesthesiologists

Table 2. Postoperative Pulmonary Complications

Pneumonia	22 (75.9)
Pleural effusion requiring drainage	8 (27.6)
Pneumothorax requiring treatment	2 (6.9)
Mucus plug atelectasis requiring bronchoscopy	2 (6.9)
Respiratory failure requiring re-intubation	5 (17.2)
Persistent air leakage requiring chest drainage	5 (17.2)

Data are presented as n (%).

P_{Imax} and IMT Variables

The P_{Imax} and IMT variables in the total group and in subjects with and without PPCs are described in Table 3. The mean P_{Imax} increased from 77.6 (SD 28.8) cm H_2O to 101.7 (SD 33.0) cm H_2O in the total group. In the group without PPCs, the mean P_{Imax} increased from 76.7 (SD 27.9) cm H_2O to 96.4 (SD 32.4) cm H_2O ($P < .001$) and from 79.5 (SD 31.2) cm H_2O to 112.1 (SD 32.4) cm H_2O in the group with PPCs ($P < .001$). No significant differences between the groups were found in the P_{Imax} values (Table 3).

The IMT was performed at an average Borg of 4.4 (SD 1.2) in the total group. In the group without PPCs, the training load increased from 40.5 (SD 17.2) cm H_2O at baseline to 55.1 (SD 18.1) cm H_2O at the last training session ($P <$ .001) and in the group with PPCs from 39.9 (SD 15.9) cm H_2O to 58.7 (SD 17.8) cm H_2O ($P < .001$). The training load as percentage from P_{Imax} at baseline increased from 54.8% (SD 14.8) to 81.0% (SD 37.5) in the group without PPCs ($P < .001$) and from 53.2% (SD 15.6) to 81.2% (SD 32.2) in the group with PPCs ($P <.001$). The mean training frequency was 2.9 (SD 1.3) times a week in the group without PPCs and 3.2 (SD 2.9) times a week in the group with PPCs. The number of training sessions was 19.7 (SD 11.7) in the group without PPCs and 22.5 (SD 12.8) in the group with PPCs. The training duration was 7.2 (SD 3.4) weeks in the group without PPCs and 8.4 (SD 4.1) weeks in the group with PPCs. No significant differences between the groups were found in intensity variables of IMT (Table 3).

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Table 3. Association of the Preoperative Maximum Inspiratory Pressure and Intensity Variables of the Inspiratory Muscle Training With Postoperative Pulmonary Complications

	Total							Corrected for Age and Pulmonary Comorbidity	
	All subjects, *n*	Mean (SD)	No PPCs, *n*	Mean (SD)	PPCs, *n*	Mean (SD)	*P*	OR (95% CI)	*P*
P_{Imax}, cm H_2O									
Baseline	79	77.6 (28.8)	53	76.7 (27.9)	26	79.5 (31.2)	.68	1.002 (0.984–1.019)	.85
Follow-up	72	101.7 (33.0)	48	96.4 (32.4)	24	112.1 (32.4)	.058	1.016 (0.998–1.033)	.07
Difference baseline-follow–up	65	22.8 (25.6)	44	18.8 (24.4)	21	31.3 (26.7)	.064	1.020 (0.999-1.043)	.066
Training load, cm H_2O									
First IMT	86	40.3 (16.7)	57	40.5 (17.2)	29	39.9 (15.9)	.88	0.996 (0.968–1.023)	.75
Last IMT	86	56.3 (18.0)	57	55.1 (18.1)	29	58.7 (17.8)	.39	1.011 (0.985–1.037)	.40
Difference first-last IMT	86	16.0 (14.7)	57	14.6 (15.0)	29	18.7 (13.8)	.22	1.023 (0.991–1.057)	.16
Mean training load	85	50.0 (17.4)	56	49.6 (17.1)	29	50.9 (18.4)	.76	1.003 (0.977–1.029)	.84
Training load related to P_{Imax}, %									
First IMT	78	54.3 (15.0)	52	54.8 (14.8)	26	53.2 (15.6)	.65	0.993 (0.961–1.025)	.66
Last IMT	78	81.1 (35.6)	52	81.0 (37.5)	26	81.2 (32.2)	.98	1.002 (0.988–1.015)	.83
Difference first-last IMT	78	26.8 (32.6)	52	26.2 (34.0)	26	28.0 (30.2)	.81	1.003 (0.989–1.018)	.65
Mean training load	77	69.9 (22.0)	51	70.2 (21.7)	26	69.5 (22.9)	.90	1.001 (0.979–1.023)	.95
Training parameters									
Training frequency per wk	84	3.0 (2.0)	55	2.9 (1.3)	29	3.2 (2.9)	.46	1.091 (0.871–1.366)	.45
Total number of training sessions	86	20.6 (12.1)	57	19.7 (11.7)	29	22.5 (12.8)	.30	1.018 (0.981–1.057)	.34
Total training period in wk	85	7.6 (3.7)	56	7.2 (3.4)	29	8.4 (4.1)	.14	1.092 (0.964–1.238)	.17

*The number of subjects varies between the analyses because of missing values in the measurements.
PPCs = postoperative pulmonary complications
OR = odds ratio
P_{Imax} = maximum inspiratory pressure
IMT = inspiratory muscle training

Corrected Association With PPCs

Logistic regression analyses corrected for age and pulmonary comorbidities and the analyses stratified for the occurrence of anastomotic leakages showed no significant association of P_{Imax} and IMT intensity variables with PPCs (Table 3 and Table S1; see related supplementary materials at http://www.rcjournal.com).

Discussion

This observational study examined whether there are associations between preoperative P_{Imax} and IMT intensity variables and the occurrence of PPCs in subjects undergoing esophagectomy. The results of this study show no significant association of inspiratory muscle strength, training load, training frequency, and training duration with PPCs in subjects with esophageal cancer who performed preoperative IMT.

In this study, we expected that IMT would lead to an increase in P_{Imax} and subsequently a reduced risk of PPCs. Consistent with this expectation, our results showed a significant improvement in P_{Imax} values after the high-load IMT period, which is in agreement with other studies showing a positive relationship between IMT and P_{Imax}.[18-20,33] However, in our study, a higher P_{Imax} was not associated with a lower risk of PPCs, even when analyses were corrected for age, pulmonary comorbidity, and the occurrence of anastomotic leakages. Of note in our study is that both subjects with and without PPCs showed an increase in the P_{Imax} during the training. The absence of an association between the P_{Imax} and PPCs in our study is in agreement with previous research in other patient groups.[20,34,35] Therefore, the question raises whether the P_{Imax} is the right outcome measure to determine an improvement in the functioning of the respiratory muscles in preoperative care.

To create more insight into the possible mechanism of action of IMT, we also investigated whether there is a relationship between intensity variables including the training load, frequency, and duration of the IMT and the occurrence of PPCs. However, our results showed no association between any of the intensity variables and PPCs. Based on these findings, the mechanism of action of IMT cannot be explained by an increase in P_{Imax} or by the intensity of the performed training. It addresses the need for better understanding and an alternative rationale for IMT. A possible explanation for the effectiveness of IMT before a major surgery[4,7,9-12,20] is that patients become more aware of their breathing during IMT. Consequently, patients may also pay more attention to breathing in the postoperative phase and have better control of their respiratory muscles, which may reduce the risk of PPCs. In line with this increased awareness and better control after IMT, patients may also be better able to perform a deep, diaphragmatic breathing pattern in the postoperative phase. This diaphragmatic breathing pattern seems important to increase alveolar ventilation, improve pulmonary function, and reduce the risk of PPCs after major surgery.[36-39] This rationale requires further investigation in future studies. Another explanation for the lack of an association between IMT variables and PPCs in our study is that IMT may be less effective in subjects undergoing an esophagectomy.[18,19] Although IMT has shown to be effective in other patient groups undergoing cardiac or major upper abdominal surgery,[4,7,9-12] there are important differences in the surgical procedures and patient population between patients undergoing an esophagectomy and other major surgery. The surgical procedure during an esophagectomy may have a more drastic effect on diaphragm function, compared to other surgical procedures.[19] Furthermore, subjects in our study had on average a relatively high preoperative physical fitness level and inspiratory muscle strength, which is in line with other studies on subjects with esophageal cancer.[19,40] Patients with a relatively good physical fitness level may benefit less from IMT than other surgical populations with lower physical fitness levels. Therefore, the added value of an IMT program for patients with lower physical fitness levels needs to be further investigated in future studies.

The results of our study seem to be generalizable to patients with esophageal cancer in clinical practice. The incidence of PPCs in this study is relatively high compared to other patient groups[1,2,41] but in agreement with other recent studies in subjects with esophageal cancer.[18-20,42,43] Furthermore, in clinical practice, the POWERbreathe Medic Plus is a commonly used threshold device, equipped with a spring-loaded valve. Therefore, the results of this study can be generalized to patients performing IMT with threshold devices with similar properties.

A strength of this study is that both the P_{Imax} and other IMT intensity variables were considered in relation to the occurrence of PPCs, which has improved insight into the possible mechanism of action of IMT in subjects undergoing esophagectomy. Another strength is that we included subjects receiving the preoperative intervention as part of the standard care pathway, preventing selection bias and resulting in a representative group of subjects. However, due to the use of data from standard care, there were missing data in the measurements; and the return of IMT logs by physiotherapists was limited, which should be mentioned as limitations in this study. Out of the 146 subjects following the complete curative treatment pathway, 59 (40.4%) subjects could not be included in the analyses because it was uncertain whether these subjects followed IMT. Despite repeated inquiries, the return of IMT logs remained relatively low. The missing data in our study were not related to characteristics of the subjects, and therefore, it is not expected that the missing IMT logs have caused serious bias in the results.

Conclusions

This study shows that a higher P_{Imax} or increase of the P_{Imax} during IMT was not associated with a reduced risk of PPCs in subjects with esophageal cancer after esophagectomy. Intensity variables of IMT were also not associated with the occurrence of PPCs after esophagectomy. Further research is needed to investigate other factors explaining the possible mechanism of action of IMT in patients undergoing major surgery, such as the awareness of using the respiratory muscles and a diaphragmatic breathing pattern.

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