Effects and Usefulness of Inspiratory Muscle Training Load in Patients with Advanced Lung Cancer with Dyspnea

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Abstract

Background

Patients with advanced lung cancer tend to develop dyspnea and the usefulness of non-drug therapy. On the contrary, inspiratory muscle training (IMT) exerts a relatively lower burden on patients; however, its usefulness has not been demonstrated. This study aimed to clarify the effects and usefulness of IMT in patients with advanced lung cancer with dyspnea.

Methods

We retrospectively analyzed 46 patients with advanced lung cancer hospitalized for medical treatment. The participants were categorized into the exercise therapy group, which served as control, and the IMT load + exercise therapy group, who performed IMT at a load of 30–40% of the maximal inspiratory pressure (MIP) in addition to exercise therapy.

Results

No patient dropped out owing to IMT load. The MIP variations had a significant interaction between group and period and that those in the IMT load + exercise therapy group increased, with significant differences between baseline and week 1, between week 1 and week 2, as well as between baseline and week 2. The analysis also demonstrated that the variations of dyspnea at rest and on exertion had a significant interaction between group and period and that those in the IMT load + exercise therapy group decreased with significant differences between baseline and week 1 as well as between baseline and week 2.

Conclusions

This study revealed that IMT load significantly improved MIP and dyspnea in patients with advanced lung cancer. In addition, the persistence rate of IMT in these patients was high.

Introduction

The general symptoms of lung cancer include dyspnea, coughing, weight loss, and chest pain.[1] Research has shown that approximately three-fourths of the patients with lung cancer experience dyspnea, with almost 90% of these patients develop dyspnea in a month preceding their death.[2] In particular, patients with advanced lung cancer who inevitably require frequent or long-term hospitalization are susceptible to the exacerbation of dyspnea at rest and on exertion. Moreover, the vicious cycle of symptoms, such as chronic dyspnea and fatigue accompanying decreased activity, is predicted to reduce their exercise

tolerance and quality of life (QOL). Dyspnea is also highly refractory to drug treatment compared to pain, and many patients with lung cancer do not achieve adequate improvement in their dyspnea.[3] Regardless of the type of treatment in lung cancer, cancer infiltration into pulmonary and surrounding tissues interrupts breathing and may induce the symptoms of dyspnea at rest and on exertion. Furthermore, regardless of the condition of the lung parenchyma, patients with advanced cancer may exhibit dyspnea due to malaise and respiratory muscle fatigue.[4]

The National Institute for Health and Clinical Excellence has recommended non-pharmacological treatment as the standard treatment method for dyspnea in patients with lung cancer.[2] In addition, pulmonary rehabilitation, which includes patient education, exercise therapy, respiratory muscle training, and nutritional therapy, has been found useful for improving dyspnea in patients with respiratory diseases.[5–7] Although limited in number, interventions have focused on the usefulness of exercise therapy as an element of pulmonary rehabilitation in patients with advanced lung cancer with dyspnea.[8] Exercise therapy has been widely reported as an element of pulmonary rehabilitation in patients with respiratory diseases, mainly chronic obstructive pulmonary disease (COPD), and a high-intensity exercise load has been recommended.[9,10] However, in the current medical setting, patients are aging and the implementation rate of high-intensity exercise therapy has declined.[11] In particular, it is very difficult for patients with advanced lung cancer to maintain their active exercise therapy and activities owing to dyspnea,[12] which accounts for the low persistence rate of high-intensity exercise therapy. On the other hand, the usefulness of inspiratory muscle training (IMT) for dyspnea is being examined in patients with cardiac failure, restrictive thoracic diseases, and neuromuscular diseases, with COPD at the forefront.[13–17] The 2015 Global Initiative for Chronic Obstructive Lung Disease guidelines state that respiratory muscle training is useful when combined with general exercise therapy.[18] Therefore, IMT load is considered to be highly suitable for patients who cannot continue high-intensity exercise therapy.[11] However, the effects of IMT load on dyspnea in patients with advanced lung cancer have not been clarified. Thus, this study investigated the effects and usefulness of IMT load in patients with advanced lung cancer with dyspnea.

Methods

Patients

In this retrospective cohort study, we analyzed 46 patients with advanced lung cancer who were hospitalized for medical treatment between April 2015 and March 2019 and who underwent rehabilitation (Fig 1). The participants were assigned either to the exercise therapy group (control) or the IMT load + exercise therapy group (intervention). Patients who underwent whole-body endurance exercise, such as ergometer riding and treadmill running; with no dyspnea at rest and on exertion; in whom the reliability of tests could not be obtained because of coughing; and with brain metastasis were excluded from the analysis.

Ethical Approval

This study was approved by the Ethics Committee of Shinshu University (approval no. 4334) and was conducted in accordance with the Declaration of Helsinki (latest version). Informed consent was obtained via the opt-out method, such that the participants had the opportunity to refuse participation in this study.

Procedures

The patients' age, sex, body mass index, cancer type and stage, performance status, Barthel index, degree of dyspnea at rest and on exertion (Modified Borg Scale [mBS] rating), type of chemotherapy, line of therapy, use of oxygen therapy, spirometry, and maximal inspiratory pressure (MIP) were retrospectively analyzed. The percentage of vital capacity, forced expiratory volume in 1 second, and forced vital capacity were measured using the Autospiro AS-407 spirometer (Minato Medical Science, Osaka, Japan) based on a previous study.[19]

Outcome Measures

MBS rating and MIP are indicators of dyspnea. Thus mBS rating and MIP were measured at three periods, namely, baseline, 1 week later, and 2 weeks later. The mBS is a subjective evaluation scale that measures the degree or intensity of dyspnea at rest and on exertion. It ranges from 0 (nothing at all) to 10 (maximal). The mBS scale was adopted as it was deemed suitable for the evaluation of the relative transitions of dyspnea.

MIP was measured as previously described[20] using POWERbreathe Medic Plus KH2 (Entry Japan, Tokyo, Japan). Maximum inspiration was determined from the level of residual air volume in the sitting position, and the pressure was maintained for 3 seconds. The measurement was performed three times, and the maximum values were adopted for analysis.[20]

Intervention

The exercise therapy did not include whole-body endurance exercise, such as ergometer riding and treadmill running, so as not to reduce the persistence rate as a result of dyspnea. The exercise therapy mainly involved activities of daily living training, including respiratory muscle stretching, upper and lower limb resistance training, basic movements, and walking, under the guidance of physical therapists.

IMT is believed to improve tolerance not only in the early stage of training but also patient satisfaction and adherence by not inducing dyspnea to a considerable extent. The IMT load + exercise therapy group performed IMT as previously described,[21,22] up to 30 times twice daily at a load of 30% to 40% of the MIP, with nose clips attached and under the guidance of physical therapists. MIP was then measured using POWERbreathe Medic Plus KH2, and the load was adjusted to the optimal loading every week.

Statistical Analysis

The clinical backgrounds of the exercise therapy group and the IMT load + exercise therapy group were compared using the χ^2 test and Student's *t* test. Variations of MIP and mBS rating were examined using 2-way repeated-measures analysis of variance (ANOVA) to investigate the effects of IMT. Mauchly's test of sphericity was used to test the assumption of sphericity; when it yielded statistically significant results, the Greenhouse-Geisser *e* correction was used to adjust violations of sphericity. In addition, the Bonferroni method was used for multiple comparisons. Statistical analysis was performed using EZR.[23] Descriptive data were expressed as mean ± standard deviation or standard error values. The significance level was set at 5%.

Results

Adherence

One patient each from the exercise therapy group and the IMT load + exercise therapy group dropped out of the study because of a deteriorated general condition due to the primary disease. No patient dropped out because of IMT load. The difference in persistence rate between the two groups, with 96.1% for the exercise therapy group and 95.5% for the IMT load + exercise therapy group, was not statistically significant (Fig 2). No difference in adherence between the two groups was observed.

Participant Characteristics

Table 1 shows the clinical characteristics of the participants at baseline. The percentage of vital capacity, forced vital capacity, and MIP of the exercise therapy group were significantly higher than those of the IMT load + exercise therapy group. No significant difference was found in the other items measured.

Two-Way Repeated-Measures ANOVA

Based on the results of the 2-way ANOVA with group and training period as the 2 factors, the MIP variations showed a significant interaction between group and period ($F = 17.14$, $P < .01$). The multiple comparisons test showed that the MIP variations in the IMT load + exercise therapy group increased, with significant differences between baseline and week 1 (33.2 ± 7.2 vs 40.3 ± 8.4), between week 1 and week 2 (40.3 ± 8.4 vs 42.2 ± 8.4), as well as between baseline and week 2 (33.2 ± 7.2 vs 42.2 ± 8.4) ($P < .01$ for all). By contrast, the MIP variations in the exercise therapy group did not show significant changes between baseline and week 1 (39.9 ± 11.2 vs 41.7 ± 9.4), between week 1 and week 2 (41.7 ± 9.4 vs 42.2 ± 8.9), as well as between baseline and week 2 (39.9 ± 11.2 vs 42.2 ± 8.9) (Fig 3).

The variations of dyspnea at rest and on exertion showed a significant interaction between group and period ($F = 8.76$, $P < .01$, at rest; $F = 13.40$, $P < .01$, on exertion). The multiple comparisons test showed that the variations of dyspnea at rest in the IMT load + exercise therapy group decreased, with significant differences between baseline and week 1 (2.3 ± 0.9 vs 1.4 ± 0.9) as well as between baseline and week 2 (2.3 ± 0.9 vs 1.3 ± 1.0) ($P < .01$ for both). By contrast, the variations of dyspnea at rest in the exercise

therapy group did not show significant changes between baseline and week 1 (2.0 ± 1.0 vs 1.9 ± 1.2), between week 1 and week 2 (1.9 ± 1.2 vs 1.8 ± 1.9), as well as between baseline and week 2 (2.0 ± 1.0 vs 1.8 ± 1.9) (Fig 4). Moreover, the variations of dyspnea on exertion in the IMT load + exercise therapy group decreased, with significant differences between baseline and week 1 (3.8 ± 0.8 vs 2.9 ± 1.0) as well as between baseline and week 2 (3.8 ± 0.8 vs 2.6 ± 0.9) (P <.01 for both). By contrast, the variations of dyspnea on exertion in the exercise therapy group did not show significant changes between baseline and week 1 (3.9 ± 1.0 vs 3.6 ± 1.3), between week 1 and week 2 (3.6 ± 1.3 vs 3.6 ± 1.3), as well as between baseline and week 2 (3.9 ± 1.0 vs 3.6 ± 1.3) (Fig 5).

Discussion

This study is the first to demonstrate the effects and usefulness of IMT load in patients with advanced lung cancer who have received medical treatment only, with the results suggesting that it could be incorporated in the non-pharmacological treatment of dyspnea in patients with advanced lung cancer. The IMT load significantly improved MIP and dyspnea at rest and on exertion in the participants. In addition, IMT was extremely useful and had a high persistence rate among the patients, who cannot undergo high-intensity exercise therapy. Notably, the IMT load improved MIP and dyspnea relatively early.

Conventionally, IMT is considered to be extremely useful for patients with decreased respiratory muscle strength. One study reported that respiratory muscle strength significantly improved in patients with an MIP value <60 cm H_2O.[11] Similarly, in 2011, Gosselink et al.[13] reported that IMT significantly improved the MIP, respiratory muscle endurance, incremental load pressure, exercise tolerance, Borg Scale rating, dyspnea (Transition Dyspnea Index), and health-related QOL of patients with COPD. In addition, the combined use of general exercise therapy and IMT has been found to significantly improve maximal inspiratory muscle strength in patients with an MIP value <60 cm H_2O.[14] These data are consistent with the findings of this study in that IMT significantly reduced MIP in the participants. Moreover, considering that dyspnea occurs in patients with advanced lung cancer as a result of malaise and respiratory muscle fatigue,[4] the improvement in MIP could have relieved the respiratory muscle fatigue of the participants and improved their dyspnea.

This study also examined the IMT period. Many studies in the past have set a relatively long intervention period (eg, 2-6 weeks of IMT for postoperative patients with lung cancer)[24,25]; in this study, significant improvement in MIP was observed as early as 1 week after IMT. In addition, significant improvement in dyspnea was observed between baseline and week 1. The clear difference between previous studies and this study is the use of surgical intervention. Research has suggested that, even in previous studies, sufficient load has not been applied in the early postoperative period owing to pain from surgical intervention and postoperative management.[26] On the other hand, postoperative effects caused by surgical intervention were not investigated in this study and the improvements in MIP and dyspnea were observed relatively earlier than in previous studies because this study targeted patients with advanced lung cancer who had received medical treatment only. Moreover, the manifestation of relatively severe

dyspnea and decreased activity as well as the large number of patients with an emergence period for post-chemotherapy myelosuppression after week 2 could have led to the early improvements in MIP and dyspnea.

A previous study defined the minimally clinically important difference of mBS ratings at rest and on exertion, which are indicators of dyspnea, as 1 in clinical settings.[27] This study also found a sufficient improvement effect, with the results indicating that the intervention has very high clinical significance. High-level inspiratory resistance training maintains small airway patency by promoting lung dilation, resulting in the possible promotion of diaphragmatic activity[28]; this forms the scientific basis for IMT. In addition, IMT has been suggested to assist in the generation of forced expiration to maintain airway clearance and to provide faster recovery of lung functions.[29] Therefore, this study inferred that IMT may (1) improve not only MIP and dyspnea but also the QOL and expectoration function of patients with advanced lung cancer and (2) help prevent subsequent respiratory complications.

Limitations of the Study

As this study was a retrospective cohort study, its outcomes are limited to the variations of MIP and dyspnea; the effects of other indicators were not investigated. In particular, more research is needed to further examine and confirm the effects of IMT on QOL and respiratory complications. In addition, dyspnea includes not only the measured values of inspiratory muscle strength but also the effects of malaise and mental functions; however, these latter factors were not investigated in this study. Studies using assessment scales for feelings of malaise and dyspnea as well as mental functions would thus be desirable.

Conclusion

This study found that IMT load significantly improved MIP and dyspnea at rest and on exertion in patients with advanced lung cancer. In addition, the effects of IMT load were observed relatively early. The findings indicate that IMT is useful and has a high persistence rate in patients with advanced lung cancer who exhibit dyspnea and cannot perform high-intensity exercise therapy.

Declarations

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[Conflict of Interest/Competing interests]

The authors have no significant conflicts of interest.

[Availability of data and material]

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

[Code availability]

Not applicable.

[Authors' contributions]

Yasunari Sakai accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Mr. Yamaga, Mr. Yamamoto, and Mr. Matsumori contributed to the data collection. Mr. Yamaga, Mr. Yamamoto, and Mr. Ikegami contributed to the statistical analysis. Mr. Ichiyama, Mr. Hanaoka, and Mr. Horiuchi have contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The authors are grateful to the paramedics, nurses, and staff of the Department of Rehabilitation at Shinshu University Hospital. The authors thank Crimson Interactive Pvt. Ltd. (Ulatus) for their assistance in manuscript translation and editing.

[Ethical approval and consent to participate]

This study was approved by the Ethics Committee of Shinshu University (approval no. 4334) and was conducted in accordance with the Declaration of Helsinki (latest version). Informed consent was obtained via the opt-out method, such that the participants had the opportunity to refuse participation in this study.

Consent for publication

Not applicable.

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Tables

Table 1 Clinical Characteristics at baseline

Variable	IMT + Exercise group (n = 21)	Exercise group (n = 25)	*P-value*
Age (years)	69.1 ± 7.1	70.7 ± 7.4	0.478
Men / women, n (%)	53 (57) / 40 (43)	29 (58) / 21 (42)	0.437
BMI (kg/m^2)	18.2 ± 1.7	18.3 ± 2.2	0.638
Type of cancer			
Non small cell lung cancer, n (%)	15 (71)	19 (76)	0.732
Small cell lung cancer, n (%)	6 (29)	6 (24)	
Cancer stage			
Stage□, n (%)	11 (52)	18 (72)	0.177
Stage□, n (%)	10 (48)	7 (28)	
PS	1.2 ± 1.2	1.3 ± 1.0	0.898
BI	92.6 ± 7.7	91.2 ± 6.9	0.515
Medication			
Line	2.7 ± 1.3	2.7 ± 1.1	0.99
Chemotherapy, n (%)	6 (29)	12 (48)	0.372
Molecular target drugs, n (%)	7 (33)	5 (20)	
ICI, n (%)	6 (29)	6 (24)	
Noting , n (%)	2 (9)	2 (8)	
Supplemental O_2, n (%)	5 (24)	4 (16)	0.517
Physiologic			
VC (%)	52.6 ± 13.4	56.7 ± 18.7	$P = 0.04$
FVC (L)	1.4 ± 0.3	1.8 ± 0.5	$P < 0.001$
FEV1.0 (%)	68.9 ± 9.1	70.1 ± 14.9	0.746
Outcome			
MIP (cmH_2O)	33.2 ± 7.2	39.9 ± 11.2	$P = 0.023$
Dyspnea at rest (mBS)	2.3 ± 0.9	2.0 ± 1.0	0.344
Dyspnea on exertion (mBS)	3.8 ± 0.8	3.9 ± 1.0	0.556

Data are counts (percentages) or mean ± SD. Definition of abbreviations: BMI indicates body mass index; PS, Performance status; BI, Barthel index; mBS, modified Borg scale; ICI, Immune checkpoint inhibitor; IMT, Maximal inspiratory pressure.

Figures

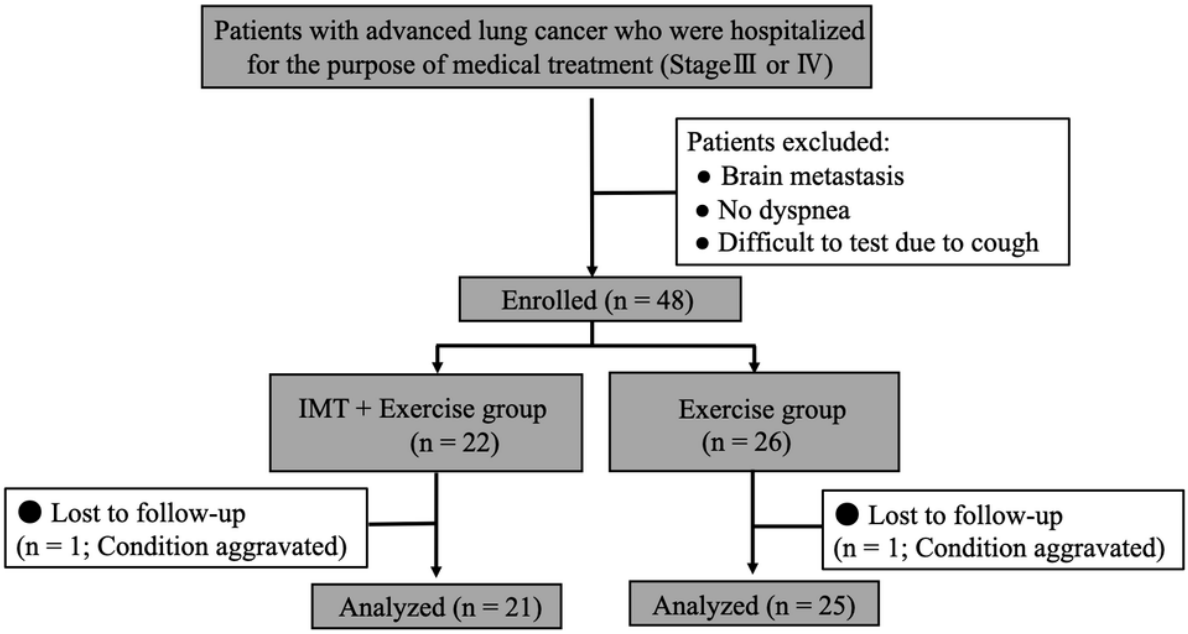

Figure 1

Flow chart of study participation. A total of 48 subjects were targeted for investigation during the study period. After exclusion criteria were applied, 46 subjects were included in the analysis.

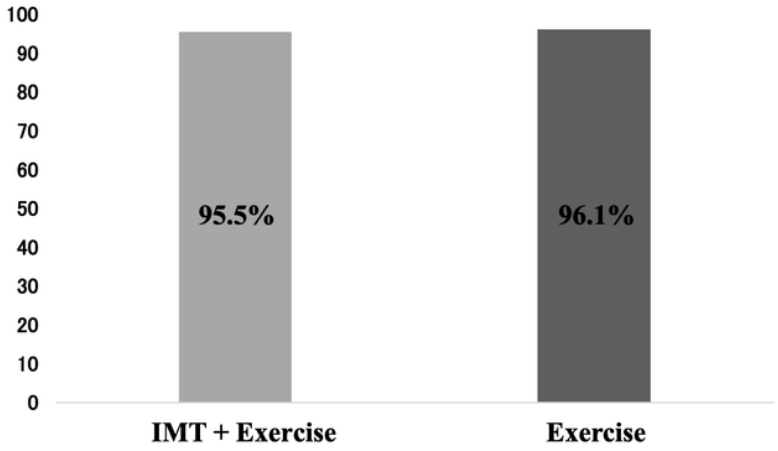

Figure 2

Treatment continuation rate of each groups.

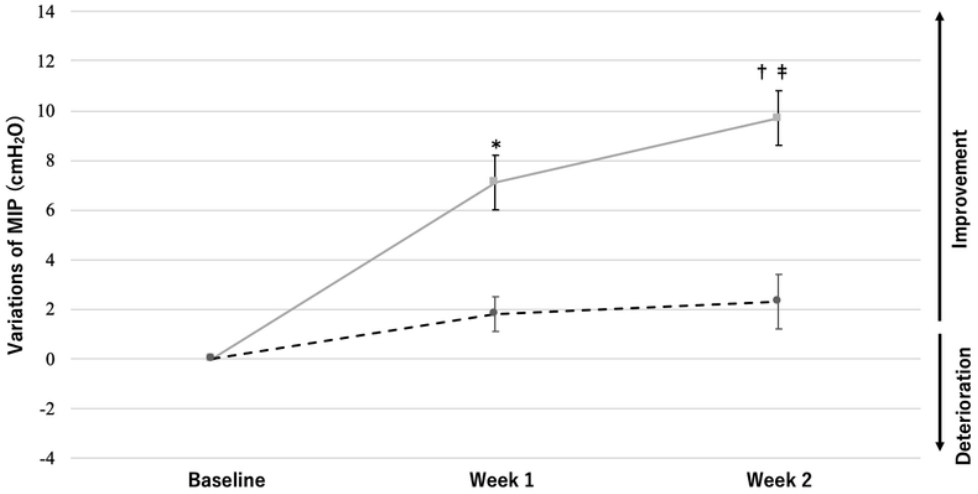

Figure 3

Effects of IMT on MIP. Data are mean ± SE. * P < 0.01, versus combined IMT group at baseline. † P < 0.01, versus combined IMT group at week 1. ‡ P < 0.01, versus combined IMT group at before intervention. T×G indicates time × group interaction.

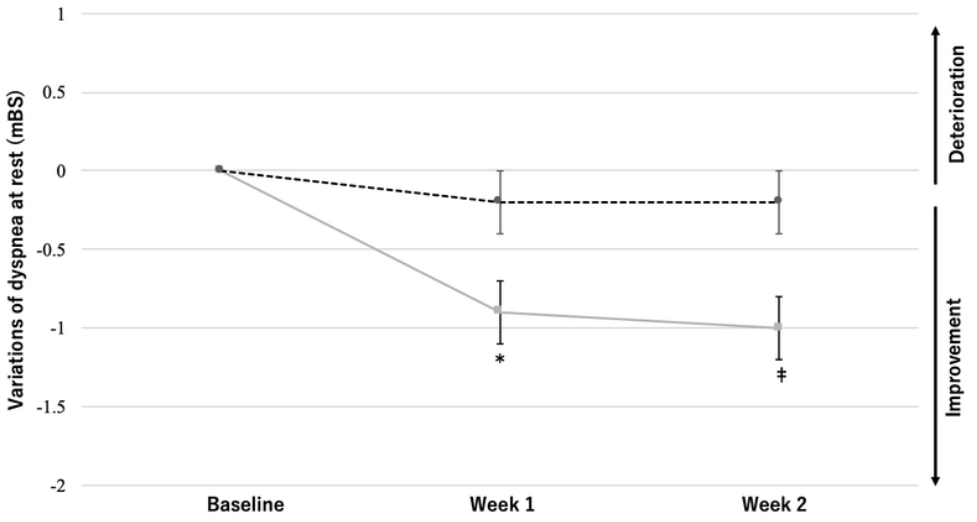

Figure 4

Effects of IMT on dyspnea at rest. Data are mean ± SE. * P < 0.01, versus combined IMT group at baseline. ‡ P < 0.01, versus combined IMT group at before intervention. T×G indicates time × group interaction.

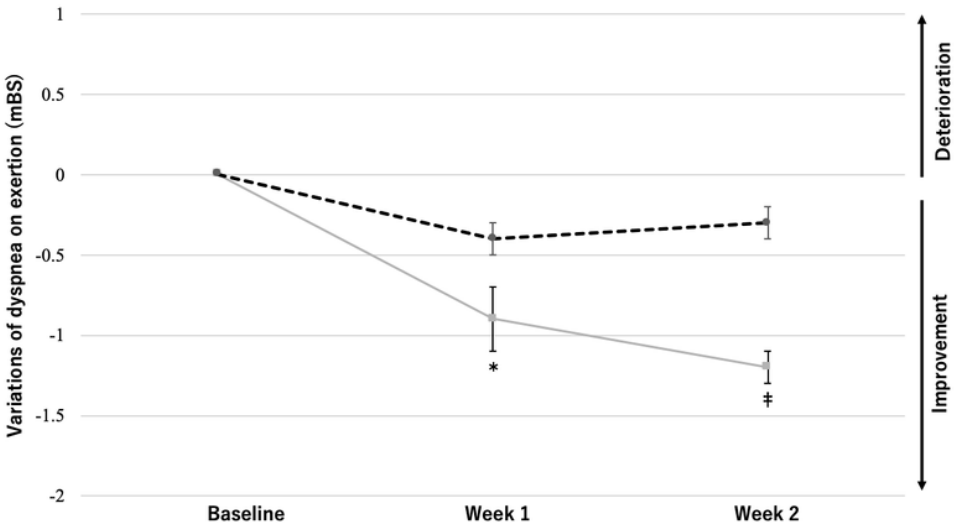

Figure 5

Effects of IMT on dyspnea on exertion. Data are mean ± SE. * P < 0.01, versus combined IMT group at baseline. ‡ P < 0.01, versus combined IMT group at before intervention. T×G indicates time × group interaction.