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Effects of inspiratory muscle training in patients with heart failure[☆]

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Summary

Aim: To investigate the effects of inspiratory muscle training (IMT) on functional capacity and balance, respiratory and peripheral muscle strength, pulmonary function, dyspnea, fatigue, depression, and quality of life in heart failure patients.

Methods: A prospective, randomized controlled, double-blinded study. Thirty patients with heart failure (NYHA II-III, LVEF < 40%) were included. Sixteen patients received IMT at 40% of maximal inspiratory pressure (MIP), and 14 patients received sham therapy (15% of MIP) for 6 weeks. Functional capacity and balance, respiratory muscle strength, quadriceps femoris muscle strength, pulmonary function, dyspnea, fatigue, quality of life, and depression were evaluated.

Results: Functional capacity and balance, respiratory and peripheral muscle strength, dyspnea, depression were significantly improved in the treatment group compared with controls; quality of life and fatigue were similarly improved within groups ($p < 0.05$). Functional capacity (418.59 ± 123.32 to 478.56 ± 131.58 m, $p < 0.001$), respiratory (MIP = 62.00 ± 33.57 to 97.13 ± 32.63 cmH₂O, $p < 0.001$) and quadriceps femoris muscle strength (240.91 ± 106.08 to 301.82 ± 111.86 N, $p < 0.001$), FEV₁%, FVC% and PEF%, functional balance (52.73 ± 3.15 to 54.25 ± 2.34 , $p < 0.001$), functional dyspnea (2.27 ± 0.88 to 1.07 ± 0.79 , $p < 0.001$), depression (11.47 ± 7.50 to 3.20 ± 4.09 , $p < 0.001$), quality of life, fatigue (42.73 ± 11.75 to 29.07 ± 13.96 , $p < 0.001$) were significantly improved in the

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treatment group. Respiratory muscle strength (MIP = 78.64 ± 35.95 to 90.86 ± 30.23 cmH₂O, $p = 0.001$), FVC%, depression (14.36 ± 9.04 to 9.50 ± 10.42 , $p = 0.011$), quality of life and fatigue (42.86 ± 12.67 to 32.93 ± 15.87 , $p = 0.008$) were significantly improved in the control group.

Conclusion: The IMT improves functional capacity and balance, respiratory and peripheral muscle strength; decreases depression and dyspnea perception in patients with heart failure. IMT should be included effectively in pulmonary rehabilitation programs.

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Introduction

Heart failure is a complex clinical syndrome manifesting as inability to supply adequate blood flow throughout the body due to any structural or functional cardiac abnormality.¹ The most common complaints are exercise intolerance, dyspnea, and fatigue in patients with heart failure. Mechanisms are multifactorial and interacting each other in patients with heart failure. Dominant catabolic process caused by left ventricular impairment, leads to respiratory and skeletal muscle myopathy. Increased ergoreflex activation caused by myopathy results in exercise intolerance.²

It is clearly stated that respiratory muscle weakness is prevalent and contributes to exercise intolerance in patients with heart failure.³ Abnormal increase in work of breathing due to excessive ventilatory response⁴ may probably contributes to dyspnea and exercise intolerance. In addition it has been suggested that central nervous system's perception of inspiratory output, increased by a signal produced by reduced inspiratory muscle strength, increases dyspnea.⁵ IMT may decrease work of breathing, metabolic costs of breathing and perception of nervous system's perception of inspiratory output, so that dyspnea and exercise capacity would be improved.

Peripheral muscle weakness also results in exercise intolerance,² and a study suggested that blood flow is distributed from respiratory to locomotor muscles during unloaded breathing.⁶ IMT may increase blood flow to peripheral muscles so that, peripheral muscle strength and also exercise capacity should be improved. To our knowledge no study investigated the effects of IMT on peripheral muscle strength. Fatigue is a frequent symptom among heart failure due to impaired cardiac pump is responsible for inadequate oxygen delivery and build up waste products from anaerobic metabolism.⁷ To our knowledge no study investigated the effects of IMT on fatigue perception. Depression is highly prevalent in heart failure and predicts worse outcomes in terms of hospital readmissions rates, functional status.⁸ Reduced physical activity enhances the peripheral and musculoskeletal pathological changes that are known to worsen heart failure symptoms and accelerate disease progression.⁹ Evidence in literature supports that depression and physical function reinforcing and changing in the same direction over time together; when one worsens, the other also worsens.¹⁰ Interventions like IMT may concurrently improve physical function and may also reduce depression and improve clinical outcomes and quality of life. No study investigated the effects of IMT on depression in patients with heart failure until now.

Advances in understanding the pathophysiology of heart failure are extending the scope and applicability of pulmonary rehabilitation in heart failure. Although numbers of studies supporting the potential benefits of IMT in different patient population, it is not generally considered in clinical practice in patients with heart failure. This may be partially due to the lack of enough evidence supporting the beneficial effects of IMT in heart failure population. In the literature, evidences are growing that IMT improves functional capacity, oxygen consumption, dyspnea and quality of life in patients with heart failure.^{11–16} However, results were differentiated due to the differences in study designs, patient selection, assessment tools and training protocols and also there is no study investigating the benefits of IMT on fatigue, depression, peripheral muscle strength and balance.

Therefore, we designed a randomized controlled and double-blinded study to investigate the effects of IMT on functional capacity, respiratory and peripheral muscle strength, functional balance, pulmonary function, dyspnea, depression, fatigue, and quality of life in patients with heart failure.

We hypothesized that IMT improves functional capacity, respiratory and peripheral muscle strength, functional balance, pulmonary function, quality of life, alleviates dyspnea and fatigue perception, decreases depression in patients with heart failure.

Materials and methods

Patients

Thirty-six patients with heart failure referred to Hacettepe University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation between June 2007 and November 2009, were included in this study. The inclusion criteria were; being clinically stable, left ventricular ejection fraction (LVEF) below 40%, New York Heart Association (NYHA) Class II and III, and no change in medications over three months. Patients with cardiac pacemaker were included after 6 weeks after implementation. The exclusion criteria were; having acute myocardial infarction, cognitive disorders, complex arrhythmias, uncontrolled hypertension, angina pectoris, recent viral infections (6 months prior to study), orthopedic problems, and rheumatologic diseases. The study was approved by the Ethics Committee of the Hacettepe University, and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients to participate in the study.

Study design

A prospective, randomized controlled, double-blinded study was performed. Prior to randomization, all patients' clinical evaluation and echocardiographic measurements were done by a cardiologist. Patients were randomly allocated to either a treatment group (18 patients) or a control group (18 patients). A computer-based program was used for randomization. All patients were taking optimal medical treatment. The treatment group received IMT, and control group received sham IMT for 6 weeks. Before and after the IMT, functional capacity, respiratory and peripheral muscle strength, functional balance, pulmonary function, dyspnea and fatigue perception, quality of life, and depression severity were evaluated.

Blinding

Neither the investigator collected pre-and post IMT data, nor the patients were aware of whether they had been allocated to treatment or control group. Patients' evaluation and treatments were performed by different physiotherapists. Treatment and controls were trained at different places and times.

Measurements

Pulmonary function tests

Spirometric measurement was performed using a portable spirometry (Spirobank MIR, Italy) according to the guidelines of the American Thoracic Society.¹⁷ Forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC), and peak expiratory flow (PEF) were expressed as the percentages of the predicted values.¹⁸

Respiratory muscle strength

Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were assessed using an electronic pressure transducer (MicroRPM; Micromedical, Kent, UK). The MIP was measured at residual volume, and MEP was measured from total lung capacity, according to Black and Hyatt.^{19,20} Reference values were used for the comparison.²⁰

Peripheral isometric muscle strength

Quadriceps femoris isometric strength was measured in a sitting position from non-dominant side, using a hand-held dynamometer (JTECH Power Track Commander II, USA). Muscle strength testing was done according to Beenakker et al.²¹ Values were expressed as the percentage of predicted values for healthy, sex and age matched subjects.²²

Functional capacity

Six-minute walk test (6MWT) was applied in a 30-m unobstructed corridor. Patients and controls were instructed to walk their own pace but to cover as much meter as possible within 6 min. Each minute standardized encouragement was given to the patients. Patients were allowed to stop and rest during test, but were instructed to go on walking as soon as they were able to do so.²³ Heart rate was monitored using a Polar heart rate monitor (PE3000 Polar Electro,

Finland) during the test. Maximum heart rate values achieved during the tests were recorded. Modified Borg Dyspnea Scale was used before and after the 6MWT. The 6MWT distance expressed as percentage of the predicted values.²⁴ The 6MWT was repeated two times. Patients were rested 30 min between the two tests, and the highest distance was recorded.

Balance

Berg Balance Scale was used to evaluate functional balance, 14 item scale, each scored 0 (lowest level of function) to 4 (highest level of function), total score 56.²⁵

Fatigue

Fatigue was evaluated using Turkish version of Fatigue Severity Scale.²⁶ It is a self-administered questionnaire, consisting of nine items. Patients were asked to rate their level of agreement with the nine statements, each item scored 0 to 7, (0: strong disagreement, 7: strong agreement). A score of 36 and above (out of a maximum of 63) indicated the presence of significant fatigue.²⁷

Depression

Depression severity was evaluated using Turkish version of Montgomery Åsberg Depression Rating Scale.²⁸ The scale consisting of 10 items, scores for each item ranging from 0–6. Low scores implied mild depression whereas high scores implied severe depression.²⁹

Dyspnea

Modified Medical Research Council dyspnea scale was used to evaluate dyspnea severity during activity. Levels of dyspnea are graded 0 (absence of dyspnea during strenuous exercise), to 4 (dyspnea during daily activities).³⁰

Quality of life

Quality of life was assessed using Turkish version³¹ of the SF-36. The SF-36 is a generic measure, consisting of eight subscales and 36 items. These subscales are physical functioning, role-physical, role-emotional, vitality, mental health, social functioning, bodily pain, general health. All subscales ranges from 0 (worst possible) to 100 points (best health). Global physical and mental health scores were calculated using subscales.³²

Inspiratory muscle training protocol

Before IMT, patients were taken in one-week familiarization period and instructed to learn breathing adequately. After, training workloads were adjusted to lower loads (20–30% of MIP for treatment group and free of pressure for control group) and patients were instructed to maintain adequate inspiration and expiration while using Threshold IMT device (Respironics, USA). As soon as the patients managed to maintain adequate workload, IMT was started. Treatment group received IMT at 40% of MIP, and training loads were adjusted to maintain 40% of the MIP, weekly. MIP was measured at supervised session each week, and 40% of measured MIP value was the new training workload. Control group received sham IMT at fixed workload, 15% of MIP. Both groups trained for 30 min-per day, 7 days per week, for 6 weeks. Once a day at each week, patients' heart rate, blood pressure and breathing frequency were monitored

during the IMT sessions and new workload was adjusted in the treatment group. Six sessions were performed at home and 1 session was supervised at the rehabilitation department in both groups. In total, 8 sessions were supervised (2 sessions in familiarization period, and 1 session at each week during 6 weeks). Patients were instructed to maintain diaphragmatic breathing, and try to maintain 10–15 breaths and rested 5–10 s between breaths. As soon as the patients managed; they were encouraged to maintain 25–30 breaths at each workload. All patients wore nose-clip during sessions. IMT diaries were checked weekly. Patients were checked by phone calls two times a week, whether they are doing IMT in a right way. Total minute spent during training period for each patient was calculated based on their reports written on diaries. Patients were told not to exercise or do physical activity over their normal routine during the study period.

Statistical analysis

All statistical analyses were performed using SPSS 15.0 statistical package (SPSS Inc., USA). Based on the results of previous study,¹¹ we estimated that a sample size of 15 patients in each group would have a power of 80% to detect 54 m difference in functional capacity for an α value of 0.05. Data normality was tested using Kolmogorov–Smirnov test. Data were expressed as mean (\pm SD) unless otherwise stated. Baseline characteristics of the two groups were compared using a Student *t*-test and differences between groups were reported as mean difference and 95%CI. Nominal data were compared using Chi-square test. ANCOVA was performed to compare the change in lung function, respiratory and peripheral muscle strength, 6MWT distance, dyspnea, fatigue, depression, and quality of life between the two groups accounting for any change in baseline variables. Manually adjusted post-hoc comparisons were done using the Bonferroni test. Statistical power and effect size were calculated using the results of 6MWT. Training efficiency, expressed as the mean improvement in MIP per hour of time spent training (expressed as $\text{cmH}_2\text{O}\cdot\text{h}^{-1}$), was calculated. A *p*-value ≤ 0.05 was considered as statistically significant.

Results

Between June 2007 and November 2009, 216 patients with heart failure were screened for the study. 180 patients were excluded because of various reasons (Fig. 1). Thirty-six patients were randomly assigned to either treatment or control group. Thirty patients (24 M, 6 F, LVEF = $34.68 \pm 7.41\%$) were completed the study, 16 patients in the treatment group, and 14 patients in the control group. 20 patients (66.7%) were in NYHA Class II and 10 patients (33.3%) in Class III. All patients were taking optimal medical therapy including beta blockers, diuretics, digoxin, and angiotensin-converting enzyme inhibitors. No significant alterations were done in medication during the study in either group. All patients tolerated IMT without any complaints, and no adverse effects occurred during evaluation and treatment. No significant changes were detected in vital signs or electrocardiographic findings in patients with pacemaker during first and following sessions. Five

patients (31.25%) in the treatment group, seven patients (50%) in the control group had no respiratory muscle weakness (MIP > 70% of predicted). Treatment group received mean $37.45 \pm 4.26\%$ of MIP, control group received fixed 15% of MIP during threshold loaded 42 sessions. Adherence to training regimen was high in both groups. There was no significant difference between the groups in terms of time spent during IMT; treatment group spent 1226.25 ± 64.69 min ($97.32 \pm 5.13\%$ of expected), control group spent 1208.57 ± 91.47 min ($95.92 \pm 7.26\%$ of expected) ($p < 0.05$). Two patients in the treatment group received IMT at 30–35% of MIP because of the Threshold IMT device, has no pressures over 42 cmH_2O .

Baseline characteristics

There were no significant differences between the two groups in baseline demographic characteristics of age, gender, NYHA functional class, weight, height, body mass index (BMI), medication, smoking, pacemaker type, and etiology of heart failure (Table 1) ($p > 0.05$). The etiology of the heart failure was predominantly ischemic in both groups. The BMI scores were over 25 kg/m^2 in 10 patients (62.5%) in the treatment group and nine patients (64.3%) in the control group. Both groups were statistically similar in terms of LVEF, pulmonary function, peripheral and respiratory muscle strength, 6MWT distance, balance, dyspnea and fatigue perception, depression severity, and quality of life (Table 1–4) ($p > 0.05$).

Inspiratory and expiratory muscle strength

MIP, MEP, %MIP and %MEP were significantly improved in both groups. Improvements in MIP (20.14 cmH_2O , 95% CI = 10.19 to 30.07 cmH_2O) and MEP (13.83 cmH_2O , 95% CI = -3.72 to 24.06 cmH_2O) were greater in the treatment group as compared with control group ($p < 0.05$, Table 2). In the treatment group MIP (33.83 cmH_2O , 95%CI = 27.85 to 40.51 cmH_2O), MEP (22.38 cmH_2O , 95%CI = 15.47 to 29.29 cmH_2O) and %MIP (41.39%, 95%CI = 30.66–52.12%), %MEP (12.96%, 95%CI = 8.81–17.1%) significantly increased. In the control group, MIP (13.69 cmH_2O , 95%CI = 6.54 to 20.85 cmH_2O), MEP (8.49 cmH_2O , 95%CI = 1.09 to 15.89 cmH_2O) and %MIP (14.69%, 95%CI = 3.19–26.17%), and %MEP (4.25%, 95%CI = -0.19 –8.68%) significantly increased ($p < 0.05$, Table 2). The IMT resulted in a mean improvement of MIP; 1.72 ± 0.76 $\text{cmH}_2\text{O}\cdot\text{h}^{-1}$ in the treatment group, 0.63 ± 0.62 $\text{cmH}_2\text{O}\cdot\text{h}^{-1}$ in the control group ($p < 0.001$).

Functional capacity

The distance covered during 6MWT (47.131 m, 95% CI = 25.78–68.49 m, Cohen $d = 0.43$) and %6MWT (7.85%, 95% CI = 4.39–11.31%) significantly improved in the treatment group compared with control group ($p < 0.05$). The distance covered during 6MWT and %6MWT significantly increased (60.37 m, 95%CI = 45.89–74.84 m; 9.80%, 95% CI = 7.44–12.16%, respectively) in the treatment group; in contrast, no significant improvements were found in the control group (13.24 m, 95%CI = -2.25 –28.72 m; 1.95%, 95% CI = -0.57 –4.47% respectively) (Table 3, Figs. 2–5). Functional capacity was also improved >54 m in four patients

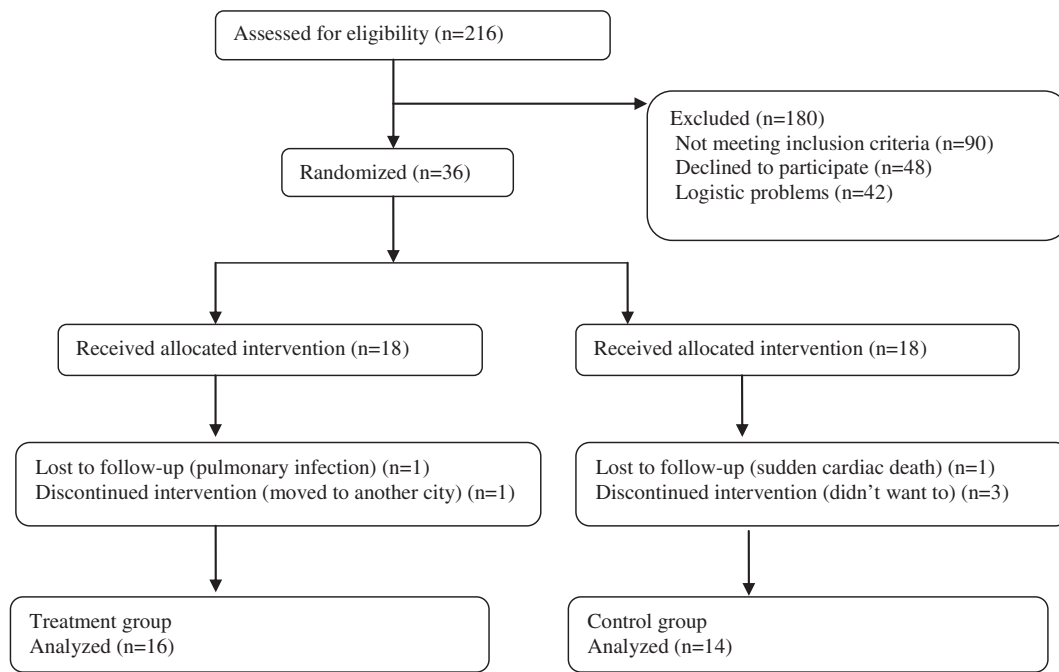


Figure 1 Flow diagram of the inspiratory muscle training.

without respiratory muscle weakness in the treatment group. No significant change was observed in maximum heart rate within and between the groups (Table 3).

Peripheral muscle strength

Improvement in quadriceps femoris muscle strength (48.47 N, 95%CI = 5.55–91.39 N) and the %quadriceps femoris muscle strength (14.11%, 95%CI = 1.41–26.81%)

were significantly higher in the treatment group compared with control group ($p < 0.05$). Quadriceps femoris muscle strength (62.96 N, 95%CI = 34.66–91.26 N), and %quadriceps femoris muscle strength were significantly improved (18.42%, 95%CI = 10.24–26.60%) in the treatment group ($p < 0.05$), no significant changes were observed (14.49 N, 95%CI = –16.89–45.88 N; 4.31%, 95%CI = –4.81–13.42%, respectively) in the control group ($p > 0.05$, Table 2).

Table 1 Baseline demographic characteristics of treatment and control groups.

Characteristics	Treatment group	Control group	Mean difference	%95 CI	p
	Mean ± SD	Mean ± SD			
Age, y	69.50 ± 7.96	65.71 ± 10.52	3.79	–3.14 to 10.71	0.27
Male/female, n	12/4	12/2			0.66
	(75%/25%)	(85.71%/14.29%)			
NYHA II/III, n	11/5	9/5			1.00
	(68.75%/31.25%)	(64.29%/35.71%)			
LVEF, %	33.43 ± 7.23	36.11 ± 7.62	–2.67	–8.23 to 2.89	0.33
Weight, kg	72.34 ± 13.56	70.20 ± 11.06	2.14	–7.20 to 11.48	0.64
Height, cm	164.50 ± 10.19	167.14 ± 8.38	–2.64	–9.69 to 4.40	0.45
BMI, kg/m ²	26.76 ± 4.30	25.08 ± 3.17	1.68	–1.18 to 4.54	0.24
Smoking, pack-years	34.89 ± 32.01	48.59 ± 33.72	–13.70	–44.84 to 17.44	0.37
Smoking (non/ex-smoker), n (%)	9/7 (56.25%/43.75%)	11/3 (78.57%/21.43%)			0.26
Medication					
ACE-I, n (%)	14 (87.5%)	12 (85.7%)			1.00
Diuretics, n (%)	11 (68.8%)	8 (57.1%)			0.51
Digoxin, n (%)	14 (87.5%)	13 (92.9%)			1.00
Beta blockers, n (%)	14 (87.5%)	12 (85.7%)			1.00
Pacemaker type					
ICD, n (%)	8 (50%)	5 (35.71%)			0.61
Biventricular, n (%)	2 (12.5%)	3 (21.43%)			
Ischemic/non-ischemic, n (%)	14/2 (87.5%/12.5%)	12/2 (85.7%/14.3%)			1.00

LVEF: left ventricular ejection fraction, ACE-I: Angiotensin-converting enzyme inhibitors, ICD: Implantable cardioverter-defibrillator.

Table 2 Effects of inspiratory muscle training on pulmonary function, respiratory and peripheral muscle strength.

Characteristics	Treatment group			Control group			Treatment affect
	Before	After	Group difference	Before	After	Group difference	
	Mean ± SD	Mean ± SD	<i>p</i>	Mean ± SD	Mean ± SD	<i>p</i>	<i>p</i>
FEV ₁ , %	84.57 ± 15.99	89.57 ± 14.55	0.024	86.75 ± 20.75	89.66 ± 19.97	0.67	0.56
FVC, %	92.07 ± 15.04	102.50 ± 15.94	0.001	91.54 ± 14.69	97.62 ± 15.27	0.023	0.46
FEV ₁ /FVC	71.15 ± 10.28	69.01 ± 11.27	0.11	71.83 ± 8.28	74.27 ± 5.85	0.073	0.020
PEF, %	73.57 ± 21.89	78.29 ± 29.06	0.049	84.08 ± 18.88	87.62 ± 17.19	0.25	0.57
MIP, cmH ₂ O	62.00 ± 33.57	97.13 ± 32.63	<0.001	78.64 ± 35.95	90.86 ± 30.23	0.001	<0.001
MIP, % predicted	66.39 ± 28.09	108.84 ± 37.11	<0.001	78.41 ± 26.26	91.88 ± 18.74	0.014	0.002
MEP, cmH ₂ O	102.63 ± 55.24	125.06 ± 56.16	<0.001	115.86 ± 43.21	124.70 ± 50.38	0.026	0.009
MEP, % predicted	54.33 ± 21.85	67.35 ± 22.89	<0.001	57.78 ± 18.01	61.96 ± 18.59	0.060	0.007
Quadriceps femoris, N	240.91 ± 106.08	301.82 ± 111.86	<0.001	291.89 ± 102.85	308.89 ± 133.02	0.34	0.029
Quadriceps femoris, % predicted	70.29 ± 22.99	88.86 ± 22.69	<0.001	86.36 ± 18.11	90.49 ± 25.17	0.33	0.031
Berg Balance Scale (0-56)	52.73 ± 3.15	54.25 ± 2.34	<0.001	54.77 ± 3.19	55.00 ± 3.23	0.17	0.034

FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; PEF: peak expiratory flow; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure.

Balance

Functional balance was significantly improved in the treatment group compared with control group (0.94, 95% CI = 0.08 to 1.79, $p < 0.05$). There was a significant increase in balance scores within the treatment group (1.36, 95%CI = 0.79 to 1.94, $p < 0.05$), in contrast to control group (0.43, 95%CI = -0.19 to 1.04, $p > 0.05$) (Table 2).

Pulmonary function

There were no significant differences in FEV₁%, FVC% and PEF% between the groups after IMT ($p > 0.05$). Change in FEV₁/FVC was significantly different between the groups, attributed to significant higher increase in FVC% in the treatment group than the control group ($p < 0.05$), no

significant change was found in FEV₁/FVC within groups. FEV₁% and PEF% were significantly increased after IMT in the treatment group ($p < 0.05$, Table 2).

Dyspnea

Dyspnea perception during activity significantly alleviated more in the treatment group as compared with control group (-0.92, 95%CI = -1.22 to -0.62, $p < 0.05$). Functional dyspnea significantly improved not only in the treatment group (-1.17, 95%CI = -1.37 to -0.96), but also in the control group (-0.25, 95%CI = -0.46 to -0.04) ($p < 0.05$, Table 3). No significant difference was found in dyspnea perception, evaluated using Modified Borg Dyspnea Scale, between groups; nonetheless dyspnea was significantly decreased within groups (Table 3).

Table 3 Effects of inspiratory muscle training on functional capacity and dyspnea.

Characteristics	Treatment group			Control group			Treatment affect
	Before	After	Group difference	Before	After	Group difference	
	Mean ± SD	Mean ± SD	<i>p</i>	Mean ± SD	Mean ± SD	<i>p</i>	<i>p</i>
6MWT, m	418.59 ± 123.32	478.56 ± 131.58	<0.001	462.31 ± 133.59	475.99 ± 135.79	0.091	<0.001
6MWT, % predicted	69.19 ± 16.59	79.00 ± 17.93	<0.001	71.16 ± 16.17	73.09 ± 15.68	0.13	<0.001
Maximum heart rate, %	65.50 ± 10.45	68.26 ± 10.09	0.43	68.75 ± 10.85	65.54 ± 9.39	0.39	0.25
Δ Heart rate, beats/min	28.20 ± 13.32	32.60 ± 9.98	0.32	33.62 ± 16.65	29.23 ± 12.61	0.41	0.21
Δ Borg Dyspnea	2.42 ± 1.73	1.42 ± 1.31	0.025	2.64 ± 1.21	1.77 ± 1.13	0.059	0.82
Modified Medical Research Council Scale (0-4)	2.27 ± 0.88	1.07 ± 0.79	<0.001	1.93 ± 0.92	1.71 ± 0.83	0.024	<0.001

6MWT: 6 min walk test.

Table 4 Effects of inspiratory muscle training on fatigue, depression, and quality of life.

Characteristics	Treatment group			Control group			Treatment affect
	Before	After	Group difference	Before	After	Group difference	
	Mean ± SD	Mean ± SD	<i>p</i>	Mean ± SD	Mean ± SD	<i>p</i>	<i>p</i>
Fatigue Severity Scale (0-63)	42.73 ± 11.75	29.07 ± 13.96	<0.001	42.86 ± 12.67	32.93 ± 15.87	0.008	0.44
Montgomery Åsberg Depression Rating Scale (0-60)	11.47 ± 7.50	3.20 ± 4.09	<0.001	14.36 ± 9.04	9.50 ± 10.42	0.011	0.054
SF-36 (0-100)							
Physical functioning	49.33 ± 29.57	68.67 ± 26.69	<0.001	57.14 ± 27.08	69.64 ± 19.06	0.002	0.47
Role-physical	35.00 ± 42.05	51.67 ± 50.41	0.053	30.36 ± 46.18	57.14 ± 48.47	0.024	0.60
Role-emotional	47.92 ± 50.14	51.11 ± 50.18	0.91	45.24 ± 48.23	59.52 ± 45.63	0.20	0.39
Vitality	56.00 ± 17.02	70.67 ± 19.99	0.001	51.07 ± 25.66	64.64 ± 24.29	0.008	0.68
Mental health	61.07 ± 19.92	76.80 ± 16.58	0.001	64.57 ± 18.29	74.57 ± 18.20	0.009	0.44
Social functioning	62.50 ± 28.74	81.67 ± 18.82	0.001	60.71 ± 22.92	88.39 ± 22.71	<0.001	0.36
Bodily pain	57.33 ± 34.94	87.83 ± 15.72	<0.001	71.79 ± 25.95	87.14 ± 20.76	<0.001	0.39
General health	44.33 ± 26.04	61.33 ± 19.87	0.001	48.57 ± 25.60	62.86 ± 23.51	0.002	0.88
Physical health sum score (0-100)	46.01 ± 28.03	67.38 ± 24.16	<0.001	51.96 ± 23.41	69.19 ± 22.06	<0.001	0.81
Mental health sum score (0-100)	57.67 ± 23.61	70.06 ± 20.91	0.004	55.39 ± 24.39	71.78 ± 21.60	0.001	0.68

Fatigue

There was no significant differences in fatigue perception between groups after IMT (-3.78 , 95%CI = -13.59 to 6.03 , $p > 0.05$) but significant differences were found within groups; in the treatment group (-13.69 , 95%CI = -20.51 to -6.87), and control group (-9.91 , 95%CI = -16.96 to -2.85) ($p < 0.05$, Table 4). There was a significant reduction in significant fatigue in the treatment group (13 patients [81.25%] to 6 patients [37.5%], $p = 0.02$), and in the control group (12 patients [85.71%] to 6 patients [42.9%], $p = 0.03$).

Depression

Depression significantly decreased after IMT between (-4.45 , 95%CI = -8.98 to -0.08) and within the groups; the treatment group (-8.77 , 95%CI = -11.89 to -5.65) and the control group (-4.32 , 95%CI = -7.55 to -1.09) ($p < 0.05$, Table 4).

Quality of life

Quality of life similarly improved in both groups after IMT. SF-36 physical functioning, role-physical, vitality, mental health, social functioning, bodily pain, and general health domains and also, SF-36 physical and mental health sum scores were significantly improved within groups after the IMT ($p < 0.05$, Table 4).

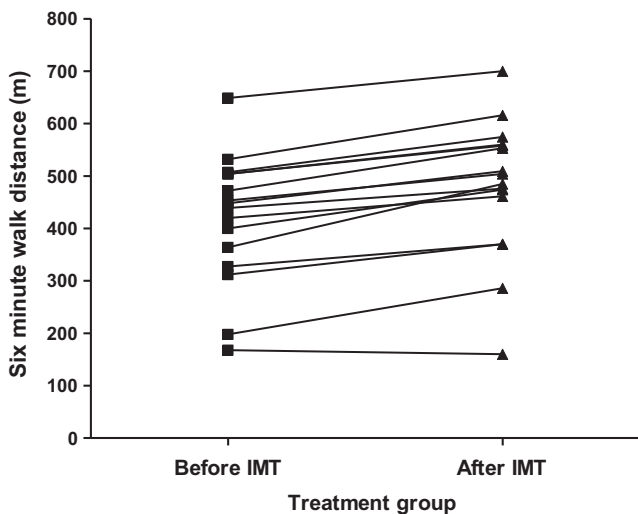


Figure 2 Six minute walk test distance before and after IMT in the treatment group.

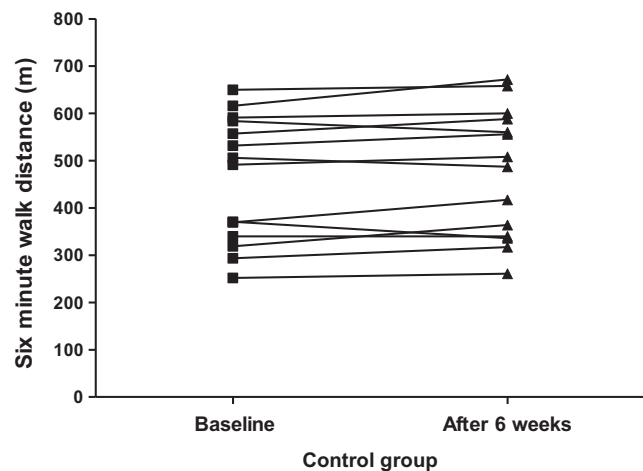


Figure 3 Six minute walk test distance before and after IMT in the control group.

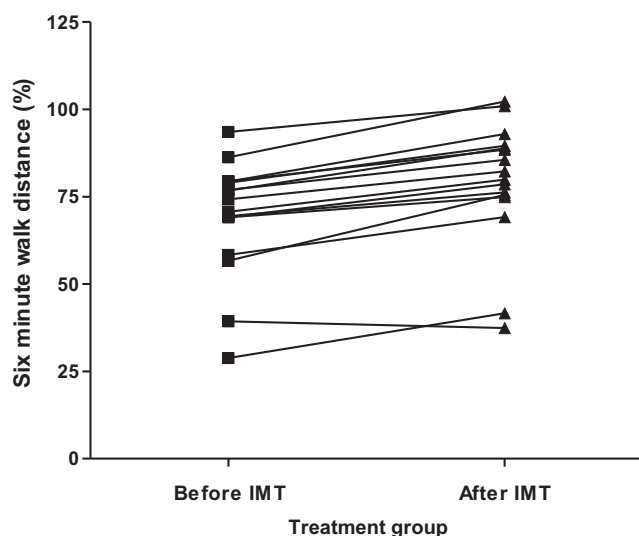


Figure 4 Percent predicted 6 min walk test distance before and after IMT in the treatment group.

Study power

The power of the present study is $(1-\beta) = 99.2\%$.

Discussion

The present study demonstrated that, IMT improves functional capacity, respiratory and peripheral muscle strength, and functional balance; alleviates dyspnea and decreases depression in patients with heart failure. Additionally, quality of life and fatigue perception were similarly improved in groups. In terms of efficacy, a six-week IMT resulted in improvement in functional capacity with high study power (99.2%). The present study has adequate sample size, control group, double-blinding to support the hypothesis. When compared with previous studies, our study has additional superiorities such as; one-week familiarization period was applied prior to IMT, and patients' adherence was strictly monitored by weekly sessions, diaries and phone calls during training period and reported. As a result, high degree

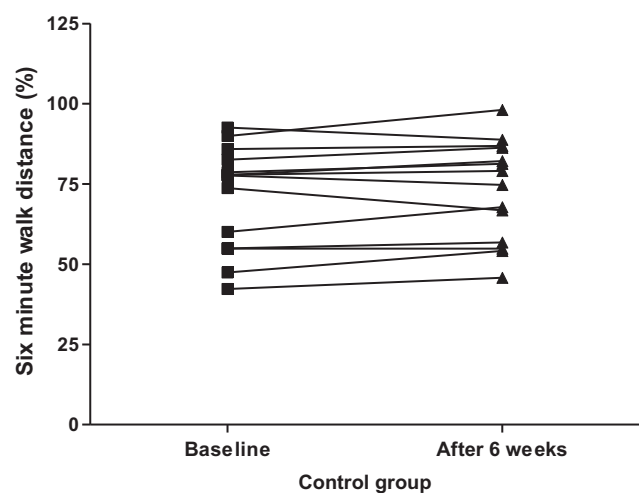


Figure 5 Percent predicted 6 min walk test distance before and after IMT in the control group.

of adherence to the training protocol yielded positive effects on investigated outcomes. In addition, this is the first report offers new information about the effects of IMT on dyspnea during daily living, depression, quadriceps femoris muscle strength and functional balance. Increase in inspiratory muscle strength resulted in clinically important decrease in dyspnea perception during daily living and depression; increase in quadriceps femoris muscle strength and functional balance, which are very important outcomes, affecting exercise capacity and quality of life in patients with heart failure.

Functional capacity

There is growing evidence that IMT improves submaximal functional capacity in patients with heart failure. Six studies investigated the effects of IMT on functional capacity evaluated using 6 or 12-min walk tests.^{11–16} The number of sessions per week and total training duration ranged from 3 to 7 days per week and 10–12 weeks, respectively. Loadings were applied ranging from 30% to 60% of MIP; 30–90 min for each session in these studies. All 6 studies reported significant improvements in functional capacity ranging from 6.9% to 29% following IMT. Three of reported higher,^{11,12,14} two reported lower increase^{15,16} in 6MWT distance compared with our study. IMT were applied for 30 min-per day, 7 days per week, for 6 weeks; the distance covered during 6MWT (59.97 ± 28.05 m, 14.5%) and %6MWT (9.11%) increased after the IMT in our study. However, a small randomized trial failed to demonstrate improvement in functional capacity using corridor walk test.³³ In consistent with previous controlled,^{11–16} randomized^{11,13} and blinded¹⁴ studies, the present study, the second randomized controlled double-blinded study proved that IMT improves functional capacity. Although all studies reported improvement in 6MWT distance only Dall'Ago et al.¹⁴ and we had calculated the adequate sample size needed. Dall'Ago et al. reported higher improvement than the present study; 42 h of IMT resulted in 22.5% increase in 6MWT distance following 21 h of IMT; 6MWT distance increased by 14.5% in our study. Longer training frequency and duration may contribute to further improvement in functional capacity, but there is still no consensus about the optimal IMT program including intensity, frequency and duration in patients with heart failure. Our findings as an important evidence supporting the current literature that IMT improves functional capacity in patients with heart failure, suggest that IMT should be implemented in the pulmonary rehabilitation programs.

Inspiratory and expiratory muscle strength

Prior studies demonstrated that IMT results in significant improvement in MIP ranging from 31.7% to 115% with and without respiratory muscle weakness in patients with heart failure.^{11–16} In accordance with these studies MIP was improved in our study. Previous studies have reported substantially lower improvement in MIP than observed in our study^{11–13,15,16} although each applied longer duration, and more rigorous workloads. These differences may be due to their small sample sizes, uncontrolled study designs, or application of IMT in patients without respiratory muscle

weakness. Only one study reported higher improvement than the present study, 42 h of IMT resulted in 115% increase in MIP.¹⁴ In our study, following 21 h of IMT, MIP increased by 56.66%. This higher increase in MIP than ours may be due to longer training duration they applied. As with other skeletal muscles, improvements in strength are likely to be dose dependent. This was the first study calculated the training efficiency in literature in patients with heart failure, IMT resulted in a mean improvement $1.72 \pm 0.76 \text{ cmH}_2\text{O}\cdot\text{h}^{-1}$ in MIP. For the better comparison of the effects of IMT on outcomes, training efficiencies should be calculated as done in this study. Further studies are needed to compare the effects of IMT in patients with and without respiratory muscle weakness for a better understanding the effects of IMT.

Peripheral muscle strength and functional balance

To our knowledge, we showed for the first time in the literature that IMT increases quadriceps femoris muscle strength and functional balance. Increase in quadriceps femoris muscle may be resulted in improvement in functional balance. A study showed that inspiratory muscle loading markedly reduces blood flow to resting and exercising limbs in heart failure patients with inspiratory muscle weakness,³⁴ and IMT improves limb blood flow under inspiratory muscle loading.³⁵ Quadriceps femoris muscle strength improvement may be due to increased blood flow after IMT, and this improvement may be resulted in decrease in ergoreflex activation and increase in exercise capacity.² This hypothesis should be confirmed. Hülsmann et al. showed that lower extremity muscle strength is an independent predictor of peak oxygen consumption (VO_2peak) in patients with heart failure.³⁶

Pulmonary function

We showed marked improvement in FVC%, $\text{FEV}_1\%$, and PEF% in the treatment group; and no differences were present between group comparisons. Change in FEV_1/FVC after IMT was different between the groups, may be attributed to higher increase in FVC% in the treatment group compared with control group. There are conflicting results in the literature related to lung function after IMT in heart failure. There are findings stating a sufficient increase in FVC% resulting decrease in FEV_1/FVC ,¹⁵ and marked increase in FVC% and $\text{FEV}_1\%$ as compared with controls,¹¹ and even no improvements in spirometry.¹⁴ Differentiation of findings from the literature may be due to our patients' lower baseline pulmonary function than that of patients included in other studies or applied different IMT workloads. In accordance with the literature, we found improvements in pulmonary function in patients who were trained $\geq 40\%$ of MIP. Higher workloads may be needed to improve pulmonary function in patients with heart failure. For better understanding of the effects of the IMT on pulmonary function, dynamic lung volumes should also be evaluated.

Dyspnea

Both groups showed similar improvements in dyspnea, evaluated using Modified Borg Dyspnea Scale in our study. We showed a reduction in dyspnea during activities of daily living after IMT, and higher workloads are needed to improve dyspnea. Our findings are important because we showed for

the first time the beneficial effects of IMT on functional dyspnea. Less dyspnea perception during functions may help patients to be more independent in activities of daily living. Most of the previous findings showed that IMT improves dyspnea evaluated using Borg Scale during submaximal and maximal exercise in patients with heart failure.^{11,14–16} Two studies failed to demonstrate these improvements in dyspnea probably due to their small sample sizes.^{12,33} A study claimed that heart failure initiates cyclical and deleterious events that impair respiratory muscle function leading to a ventilator challenge the system is unfit to meet, which further deteriorates respiratory function.³⁴ IMT may be cutting this vicious cycle and reducing dyspnea.

Fatigue and depression

In literature for the first time, we investigated the effects of IMT on fatigue perception. Although fatigue was alleviated in both groups, higher IMT workload was not superior to lower workload. Lower workloads may also have therapeutic effect in reducing fatigue, thus further studies are needed investigating the effects of IMT on fatigue. Improvement in peripheral blood flow,³⁵ quadriceps femoris muscle strength and functional capacity after IMT may be resulted in decreased fatigue. Depression among patients with heart failure is higher than expected among other chronically ill patients and linked to more severe heart failure symptoms and worse outcomes.³⁷ Ours was the first study investigating the effects of IMT on depression in patients with heart failure, and we showed that IMT decreases depression.

Quality of life

Previous findings of two studies^{11,14} proved that IMT improves quality of life evaluated using Minnesota Living With Heart Failure Questionnaire (MLWHF), a disease-specific quality of life scale. In the present study both groups showed similar improvement in quality of life measured using a generic quality of life scale SF-36. Only one domain of SF-36 (role-emotional) was not improved. This domain investigates the role limitations in work, and nearly all patients were retired. Previously studies showed that quality of life improved only in treatment group, both groups' quality of life improved in our study. These different findings may be due to the better performance in detecting changes in patients who are elderly and have high comorbidity, including larger number of health dimensions of SF-36 than MLWHF Questionnaire, as claimed by Zuluaga et al.³⁸ As many outcomes also improved in the treatment group, all these improvements may be resulted in increased quality of life.

In the literature, there is only one case report showed the beneficial effects of IMT in heart failure patients with pacemaker.³⁹ In the present study ten patients (62.5%) in the treatment group, nine patients (64.28%) in the control group had pacemaker and no adverse effect occurred during treatment and IMT resulted in improvements in several outcomes.

Limitations

Some researchers believe that IMT should be applied to the heart failure patients with inspiratory muscle weakness. We included 12 patients (40%) without inspiratory muscle weakness in our study. Three studies^{11,15,16} done by the same researchers, proved that IMT improves inspiratory

muscle strength and functional capacity in patients without inspiratory muscle weakness. New studies should be conducted, to compare the outcomes in heart failure patients with/without inspiratory muscle weakness for better understanding the effects of IMT. Despite the documented benefits of IMT in patients with heart failure, previous and present study have not been investigated the longer-terms affects on outcomes and survival. The etiology of the heart failure was predominantly ischemic; the number of patients with male gender was high. As in literature, we used threshold loading 15% of MIP as a sham therapy, thus many outcomes improved in sham group, may be because of; 15% of MIP loading may have therapeutic effects. Selecting lower workloads as a sham therapy will/would be better while investigating the effects of IMT.

Clinical relevance and future directions

The present study contributes new information to the knowledge regarding the benefits of IMT on functional capacity, peripheral muscle strength, functional balance, quality of life, fatigue and depression. The current results advice IMT may be beneficial to all outcomes stated. From a patients' perspective quality of life, fatigue, dyspnea and depression are unarguably the most important outcomes. Since these outcomes improved following IMT, we believe that this alone justifies the inclusion of IMT to rehabilitation programs. Achieving to higher training loads was difficult due to intolerable dyspnea at the beginning and during the IMT in patients with heart failure in this study. Most of patients couldn't manage to train 40% of MIP at the beginning of IMT, for this reason a familiarization period should be applied before IMT. Dyspnea is the most limiting factor of exercise in patients with heart failure; IMT may be applied before exercise training to tolerate exercise well. Interval-based IMT programs may offer opportunity to achieve higher training loads with dyspnea, although no study has investigated up to now. Based on the result of this study, as no adverse effect occurred during treatment we suggest that IMT should be included as a safe intervention in rehabilitation programs in heart failure patients with pacemaker.

Conclusions

This randomized, controlled, double-blinded study demonstrated that, IMT improves functional capacity, respiratory and peripheral muscle strength, and functional balance; alleviates dyspnea and decreases depression in patients with heart failure. Although similar improvements were observed in quality of life within groups, based on the current literature we believe that IMT improves quality of life.

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Conflict of interest

There are no conflicts of interests for any of the authors for this work.

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