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Systematic Review

THE BENEFITS OF INSPIRATORY MUSCLE TRAINING IN HEART FAILURE PATIENTS: A SYSTEMATIC REVIEW

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Abstract

Background: Patients with heart failure (HF) have impaired function of respiratory system and frequently experience dyspnea. Inspiratory muscle training (IMT) offers an alternative way of exercise with a lot of benefits for HF patients.

Aim: The aim of this review was to summarize and to reveal the effects of IMT in HF patients.

Methods: Electronic searches were performed using Pubmed Database, Physiotherapy Evidence Database (PEDro) and Cochrane Library. Inclusion criteria were: RCTs, patients with HF, full text articles after 2010 and at least one intervention group with IMT. Methodological quality was assessed using the PEDro (Physiotherapy Evidence Database) scale.

Results: Nineteen articles met the inclusion criteria and were included in this review. In most studies training protocols involved 3 to 7 sessions per week with intensity ≤30-60% of maximal inspiratory pressure (MIP), for a total duration of 4-12 weeks. Respiratory muscle strength improved in 11/12 studies, peripheral muscle strength in 4/5 studies, exercise capacity (peak VO_2, VE/VCO_2 slope) in 4/10, pulmonary function (FEV_1, FEV_1/FVC, FVC) in 0/5, functional capacity (6MWT) in 6/8, echocardiography parameters in 1/6, quality of life and dyspnea in 9/16. Control groups followed sham IMT, usual care, no intervention, intervention without exercise, or aerobic training, which could explain in some cases the conflicting results.

Conclusions: IMT is beneficial for HF patients and should be included as a complementary method in cardiac rehabilitation programs. The optimal characteristics of IMT as well as the benefits when combined with common forms of exercise need further research.

Keywords: Inspiratory muscle training, respiratory muscle training, inspiratory resistance training, breathing exercise, heart failure.

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INTRODUCTION

Chronic heart failure (CHF) is a complex disease characterized by a wide range of symptoms (e.g. dyspnea, muscle fatigue) and signs (e.g. pulmonary dysfunction, abnormal breathing patterns).[1,2] Several skeletal muscle and respiratory abnormalities including impaired resting lung function, peripheral muscle microcirculation and inefficient ventilation have been identified in CHF patients that probably play an important role in the pathophysiology of exercise intolerance.[3-5] Also, CHF patients demonstrate increased respiratory drive at rest and abnormal breathing pattern during exercise which is associated with disease severity.[6] Moreover, patients with CHF present impaired inspiratory muscle strength and endurance, an additional factor which is associated with limited exercise and poor prognosis.[7] There is evidence of benefits from IMT applied in CHF patients, including improvement of respiratory muscle strength, functional capacity, ventilation, quality of life and decreased dyspnea.[8-12]

The aim of this review is to summarize and shed light on the effects of IMT in CHF patients, as well as to provide more reliable estimates regarding the usefulness of respiratory training as a complimentary method in the HF rehabilitation programs.

METHODOLOGY

Data sources

The literature research was performed in the following electronic databases: Pubmed, Cochrane library and Physiotherapy Evidence Database (Pedro). The keywords used in the search were: inspiratory muscle training, IMT, respiratory muscle training, respiratory exercise, inspiratory resistance training, breathing exercise, heart failure, CHF. These terms were appropriately combined using the booleans OR and AND. For example, the search strategy in Pubmed database was as follows: (Inspiratory muscle training OR IMT OR Respiratory muscle training OR Respiratory training OR Respiratory exercise OR Inspiratory resistance training OR Breathing exercise) AND (Heart failure OR CHF). The search was restricted by the following criteria: Clinical Trials, Full Text studies, humans and English language, using appropriate filters.

Eligibility Criteria and Data Collection

We included studies with or without combined exercise programs. Inclusion criteria were the following: 1) RCTs, 2) HF patients, 3) full text articles, 4) articles published after 2010. Exclusion criteria were: 1) animal studies, 2) languages other than English.

Our data presented patient characteristics (number of patients included, age, gender, diagnosis and disease severity), intervention (type, duration, frequency, resting period) and outcomes related to respiratory muscle strength, pulmonary function, exercise capacity, peripheral muscle function, functional capacity, quality of life and dyspnea.

Methodological quality

The methodological quality of the studies was evaluated by the PEDro scale. The Pedro scale is based on 11 items to assess scientific rigor related to eligibility criteria, allocation, baseline between-group comparability, blindness of subjects, therapists, and assessors, follow-up, statistical analysis, and results reporting[13]. Based on the total score, studies were categorized as high- (> 5), moderate- (4-5), or low- (< 4) quality.

RESULTS

Study selection

The initial search led to retrieval of 1798 articles. After 1350 duplicates were removed, 450 records were screened at abstract level. The full text of 31 studies was assessed for eligibility. Of those 31 studies, 12 were excluded being published before 2010. Finally, 19 RCTs were included in the present review.[14-32] The PRISMA flow diagram is presented in figure 1.

Methodological quality

The Pedro score for the included studies is presented in Table 1. The score ranged from 5 to 8 (that is, moderate to high quality). The allocation of subjects was concealed in 6 studies.[14,20,21,24,27,31] Furthermore, all the studies provided baseline data ensuring between-group comparability. All the studies met the follow up criteria as described by Pedro scale. Ten of the studies were of high methodological quality (PEDro score>5)[14-17,20,23,26,27,31] and nine studies were of moderate quality (PEDro score

=5).[18,19,22,24,25,28,29,30,32] The level of evidence could be considered as moderate to strong.

Participants

The characteristics of the patients included in this systematic review are presented in Table 2. We included data that were relevant for at least one of the main outcomes of interest. Data from 726 patients were analyzed. Disease severity was categorized by the NYHA classification. Two studies had CHF patients with preserved ejection fraction.[26, 27] The remaining 17 studies had CHF patients with reduced ejection fraction. One study investigated stroke patients with stable CHF[23] and another study included patients with implanted left ventricular assist device.[16] Inspiratory muscle weakness was identified in some of the patients included in the study (MIP<70% of the predicted value).[14,19, 21,23]

Interventions

The characteristics of the interventions are shown in Table 2. IMT duration ranged, in most studies, from 4 to 12 weeks.[14-24,26,28] One study lasted 4 months.[25] Two studies started with 10-12 weeks IMT, followed by 10-12 weeks usual care (crossover studies).[29,31] Three studies used follow up evaluation: one study at 5 months[30] and two studies at 6 months.[27,32] Concerning the load, 9 studies used loads > 30% to 60% of maximal inspiratory pressure (MIP) or sustained MIP (SMIP).[15-18,20-23,25] One study used training loads which allowed the performance of 10 consecutive maximal repetitions (10RM), so the training intensity was 100% of their 10 RM.[14] Five studies used load ≤30% of MIP.[19, 21, 24, 26, 27] Frequency of training ranged from 3 to 7 times per week with duration of each session, mostly, up to 30 minutes, with 1 or 2 sessions per day and with a common respiratory rate of 15-20 breaths/min. In relation to the training methods employed, IMT was performed using an inspiratory muscle trainer with training loads adjusted to the inspiratory pressure,[14-27] or using a device-guided slow breathing via the introduction of low and high-frequency tones to entrain exhalation and inhalation,[28,29,31,32] or using deep and slow diaphragm breathing training according to voice-guided directions.[30]

Concerning the control groups, patients performed IMT with low or no respiratory load,[14,17,19-21] aerobic training,[15,16] combined training (aerobic with IMT or with strength exercises),[18,22] usual care treatment,[26,27,29,31] intervention without exercise[23,28,30] and no intervention.[24,25]

Functional assessments

Respiratory muscle strength

Five studies evaluated the effect of combined exercise/IMT vs. control group on respiratory muscle strength;[15,16,18,22,24] MIP improved in two studies,[22,24] SMIP[15,18] improved also in two studies, maximal expiratory pressure (MEP) improved in one study,[24] whereas nonsignificant differences were observed in MIP in three studies[15,16,18] and in SMIP in one study.[16] Seven studies[14,17,19,21,23,25,26] examined IMT alone with no other form of exercise training; intervention groups demonstrated significant improvement in MIP (all studies) and in MEP (two studies),[14,17] compared to control groups, while no significant differences were found in MEP in one study.[23]

Peripheral muscle strength

Five studies assessed peripheral muscle strength.[14,15,17,22,24] Three studies[15,22,24] used combined exercise/IMT vs. control group and evaluated lower limb muscle strength (quadriceps femoris). The results revealed significantly higher muscle strength and endurance in the treatment groups compared with the control groups. The remaining two studies[14,17] examined IMT alone with no other form of exercise training, with conflicting results. One study[14] evaluated upper limb muscle strength (handgrip strength) and revealed no significant differences between groups, while the other one[17] found greater improvement of peripheral muscle strength and functional balance in the treatment group compared to controls.

Pulmonary function

Five studies[16-18,23,24] evaluated the effect of IMT on pulmonary function, mostly employing: forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC; no significant differences were observed between the intervention and control groups.

Exercise capacity

Six studies assessed the effects of combined exercise/IMT vs. control group using cardiopulmonary exercise testing (CPX).[15,16,18,22,26,27] Variables mostly employed were peak oxygen uptake (peak VO_2), ventilation/carbon dioxide slope, VE/VCO_2 slope and VE. Four of these studies[15,16,18,22] revealed no significant differences in most CPX parameters between the intervention and control groups, whereas the other two studies[26,27] found significant improvement of CPX parameters in the trained patients.

Five studies investigated the effects of IMT alone with no other form of exercise training vs. control group[19,21,25,27,32] on cardiopulmonary function. Two studies revealed no significant differences between the intervention and control groups in most CPX parameters.[19,32] In the remaining three studies, trained patients presented significantly improved CPX parameters compared to controls.[21,25,27]

Echocardiographic parameters

Four studies evaluated the effects of combined exercise/IMT vs. control group on echocardiographic parameters and reported no significant differences between the intervention and control groups.[15,18,26,27] Three studies[27,31,32] evaluated the effects of IMT alone with conflicting results; one study[31] reported significant improvement in most echocardiographic parameters, while the other two studies[27,32] reported no significant changes in echocardiographic parameters.

Functional capacity

Four studies[16,24,26,27] assessed the effect of combined exercise/IMT vs. control group on functional capacity using the six minute walk test (6MWT). Conflicting results emerged. Three studies[24,26,27] found that the distance covered during the 6MWT significantly increased in the treatment groups compared to control groups, whereas one study[16] found no significant differences between groups. Five studies[17,27,30-32] used IMT alone and all but one[30] showed significant improvement in the treatment groups compared to control groups.

Quality of life and dyspnea

Seven studies[15,16,18,22,24,26,27] evaluated the effect of combined exercise/IMT vs. control group on quality of life (Qol) and dyspnea using several assessment methods. Three studies found no significant changes in Qol[16,22,24] and dyspnea[16] between the intervention and control groups, whereas four studies reported significant improvement in Qol[15,18,26,27] and dyspnea[15,18] in the intervention compared to control groups. Ten studies used IMT alone[14,17,19-21,25,27-30] with conflicting results; four studies found no significant differences between the intervention and control groups regarding Qol[14,17,29] and dyspnea[14,28,30] while in six studies the intervention groups showed significant improvement in Qol[19,21,25,27] and dyspnea[17,19,20] compared to control groups.

Functional classification

Three studies[15,18,24] assessed the effect of combined exercise/IMT vs. control group on functional status using the New York Heart Association (NYHA) classification and reported no significant differences between the intervention and control groups. Two studies[20,28] used IMT alone with conflicting results; NYHA class improved in the training group compared to the control group in one study,[20] while the other one[28] did not show significant differences between groups.

DISCUSSION

This systematic review indicates that IMT, isolated or combined with other forms of exercise training, improves respiratory and peripheral muscle strength, whereas it seems to have no effect on pulmonary function. Furthermore, the included studies demonstrate conflicting results after IMT application regarding the other parameters of interest: exercise and functional capacity, echocardiographic parameters, quality of life and dyspnea. The results were varying among the studies likely because of the different loads (adjusted for MIP/SMIP), the method employed, i.e., *threshold IMT, device-guided breathing and diaphragmatic exercises,* the frequency and duration of intervention as well as the small sample size of the studies. The best mode and training method of IMT is not clear.

All the studies which performed IMT based on SMIP revealed non-significant differences in MIP; utilization of SMIP adjusted load seems to improve the respiratory muscle endurance and not the MIP.[15,16,18] This could possibly explain, at least partly, the conflicting results. Analysis of the studies showed that IMT at a low percentage load (≤15% of MIP)[14,17,19] was not enough for the control groups to reach the same improvements as the intervention groups which used training loads ≥ 30% of MIP. Another study came to the same conclusion, comparing the effect of low intensity training (15% of MIP) and moderate intensity training (30% of MIP); it was shown that only the moderate intensity exercise training improved MEP and NYHA functional classification.[24]

IMT when combined with a specific program of lower limb muscle resistance training improved peripheral muscle strength.[15,22,24] IMT when performed without other form of intervention improved also peripheral muscle strength; although this result is a clear indication of an autonomous beneficial effect of this type of exercise training (i.e. IMT) on peripheral muscle strength,[17] there is a need for further research for its final documentation. In another study which used IMT alone, upper limb muscle strength (handgrip strength) did not correlate with MIP.[14]

All studies, regardless of using IMT alone or combined with other form exercise training, presented no differences in pulmonary function in between-group comparisons.[16,17,18,23,24] This result may be due to the relatively good functional status of the lungs at baseline or because of an inappropriate training method, unable to improve the spirometric parameters (FEV_1, FEV_1/FVC, FVC). NYHA status improved in all studies but one;[28] the duration and respiratory rate of the device-guided breathing exercise technique could probably account for the result.

Although studies revealed within group improvements in exercise capacity, functional capacity, quality of life and dyspnea after IMT, results were varied in terms of between-group comparisons; in several studies no differences were noted between the intervention and control groups regarding peak VO_2 and VE/VCO_2 slope,[15,16,18,19,22,32] 6MWT,[16,30] as well as quality of life and dyspnea;[14,16,22,24,28-30] this may be due to the fact that in some cases not only the intervention but the control groups also incorporated aerobic exercise in their training programs or they had almost the same training characteristics (duration, rest, sham-IMT). Furthermore, echocardiographic parameters[15,18,26,27,32] were not improved in almost all studies.

Patients with preserved ejection fraction[26,27] showed remarkable improvements in functional capacity, exercise capacity and quality of life, as patients with reduced ejection fraction. Follow up evaluations[27,30,32] also, revealed that IMT beneficial effects are maintained in most outcomes of interest.

Different training methods may lead to different results: some studies utilize a Threshold IMT breathing trainer for continuously providing a specific resistance (e.g. 30% of MIP) which is controlled, i.e. determined by the training supervisor; in contrast, other studies use other exercise techniques that focus on slow and deep inhalations according to recorded instructions.

Heart and lungs are interconnected, being parts of the system that supplies oxygen to the body organs and tissues. However, peripheral muscle dysfunction and inspiratory muscle weakness seems to be involved in the underlying mechanisms for fatigue, dyspnea and exercise intolerance in patients with HF. At rest and during exercise HF patients hyperventilate, causing structural and biochemical alterations in diaphragmatic muscle.[33] The effect of IMT on respiratory system, functional status and quality of life in patients with HF has been studied by many researchers. Potential mechanisms, underlying the effects of respiratory training, include increased ventilatory efficiency, lower oscillatory ventilation during incremental exercise, improved recovery oxygen uptake kinetics, as well as reduced sympathetic nervous activity.[8,21] The use of IMT, also, attenuates the mechanisms involved in respiratory muscle metaboreflex in CHF patients, improving blood flow in peripheral muscles during inspiratory loading, in resting and exercising limbs.[19,34]

In a previous review by Lin et al,[35] which included studies with isolated or combined IMT, it was shown that IMT significantly improves respiratory muscle strength and functional capacity, whereas, the effect of IMT on quality of life was inconsistent; this could be due to the different evaluation questionnaires being used. The improvement in inspiratory muscle strength could be translated to an improvement in functional capacity as CHF patients demonstrate low functional capacity due to respiratory fatigue and dyspnea.[8,36]

In another review by Neto et al,[37] combined exercise along with IMT offered additive benefits in quality of life compared with conventional aerobic training alone although, no extra benefits were established regarding the exercise capacity. This improvement in quality of life may be related to the benefits of IMT in cardiovascular and respiratory response as well as in the reduction of dyspnea.

Limitations

There were several limitations in the articles we reviewed. Initially, the sample size in all studies was small. There is a need for more randomized controlled trials in future with well-defined protocols and larger samples. Articles with device-guided paced breathing in HF patients were limited, as well as studies in patients with preserved ejection fraction and follow up evaluations. In addition, the improvement identified in the control groups in respiratory muscle strength probably occurred because they used IMT at a low percentage of MIP as sham therapy. It would be better if all the studies were designed without any training load in their control groups.

CONCLUSIONS

There is substantial evidence that IMT in patients with HF increases respiratory and peripheral muscle strength and seems to be beneficial regarding functional capacity, exercise capacity, quality of life and dyspnea. IMT should be part of a cardiac rehabilitation program as a complementary method, considering its safety and the demonstrated positive effects. The optimal characteristics of IMT as well as benefits when combined with common forms of exercise need further research. Also, more follow up evaluations are needed to explore the long term effects of respiratory training in patients with heart failure.

Conflict of interest:
Authors declare that there is no conflict of interest.

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ANNEX

Figure 1. Flow diagram of search strategy.

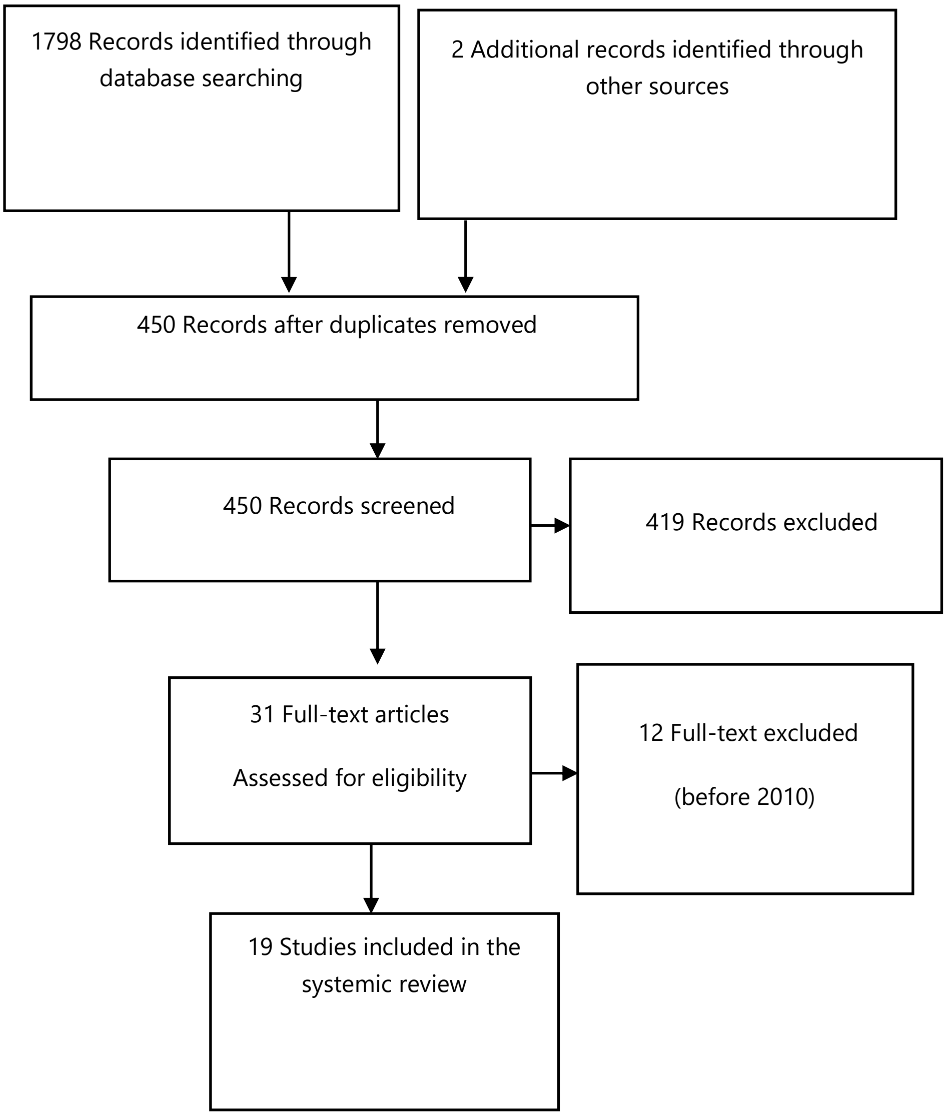

TABLE 1. Methodological quality of the studies included in the systemic review (Pedro scores)

	Random allocation	**Concealed allocation**	**Baseline comparability**	**Blinded subjects**	**Blinded therapists**	**Blinded assessors**	**Follow-up**	**Intention-to-treat**	**Between-group analysis**	**Point estimates and variability**	**Total score**
Bosnak-Guclu et al,[17] 2011	√		√	√		√	√		√	√	7
Ekman et al,[28] 2011	√		√				√		√	√	5
Laoutaris et al,[16] 2011	√		√			√	√		√	√	6
Mello et al,[21] 2012		√	√		√	√	√			√	6
Laoutaris et al,[15] 2013	√		√			√	√		√	√	6
Marco et al,[14] 2013		√	√	√	√	√	√		√	√	8
Palau et al,[26] 2014	√		√			√	√		√	√	6
Adamopoulos et al,[18] 2014	√		√				√		√	√	5
Drozdz et al,[29] 2015	√		√				√		√	√	5
Seo et al,[30] 2015	√		√				√		√	√	5
Chen et al,[23] 2016	√		√			√	√		√	√	6
Kawauchi et al,[24] 2017		√	√				√		√	√	5
Kawecka et al,[31] 2017		√	√		√		√		√	√	6
Moreno et al,[19] 2017	√		√				√		√	√	5
Palau et al,[27] 2020		√	√			√	√	√	√	√	7
Hornikx et al,[22] 2020	√		√				√		√	√	5
Hossein Pour et al,[20] 2019		√	√	√	√	√	√		√	√	8
Lachowska et al,[32] 2019	√		√				√		√	√	5

Antunes-Correra et al,[25] 2020	√		√				√		√	√	5

TABLE 2. Intervention characteristics, parameters, outcomes and main results of the studies which included in this review

Study	Sample of intervention/ control group	Interventions by group/side		IMT parameters	Study Measurements				
					Functional assessments				
		Control group	Experimental group		Peripheral muscle strength	Respiratory muscle strength	Exercise and functional capacity	Pulmonary function	Quality of life, dyspnea & echocardiography parameters
Marco et al,[14] 2013	22 CHF Exp= 11 Age: 68.5±8.88 yr Con= 11 Age: 70.1±10.75 years NYHA: II-III	Sham-IMT	IMT	4 wk IMT F: 2x/d, 7d/wk 5 set/10 rep R: 1-2 min RR:15-20 breaths/min Exp: I: 10 consecutive max inspirations (10RM)-100% of their 10RM Con: I: 10 cmH_2O & ↑ 2.5 cmH_2O/wk	Exp: ↔ in upper limb muscles Con: ↔ in upper limb muscles Between groups: ↔ in upper limb muscles	Exp: ↑MIP, ↑MEP Con: ↔ MIP, MEP Between groups: Exp ↑MIP, ↑MEP Vs Con			Exp: ↓dyspnea ↔ Qol Con: ↔ Qol, dyspnea Between groups ↔ Qol, dyspnea

Laoutaris et al,[15] 2013	27 CHF Exp= 13 Age: 57.1±11 yr Con= 14 Age: 58.6±8 yr NYHA: II/III	AT	ARIS (AT/RT/ IMT)	12 wk F: 3x/wk AT: bike exercise 70-80% of max HR T: 30 min for Exp and 45 min for Con group Exp: RT: I: 50% of 1RM 3set/10-12 rep (quadriceps resistance exercises) 2set/10-12 rep (upper limb exercises) T: 15 min R: 2 min IMT: I: 60% of SMIP T: 20 min	Exp: ↑QMT peak, ↑QME, ↑1RM Con: ↑QME ↔ QMT peak, 1RM, Between groups: Exp ↑QMT peak, ↑QME, ↑1RM Vs Con	Exp: ↑MIP, ↑SMIP Con: ↑MIP ↔ SMIP Between groups: Exp ↑SMIP, ↔ MIP Vs Con	Exp: ↑peak VO$_2$, ↑exercise time ↑VT, ↑CP, ↓VE/VCO$_2$ slope ↔ RER, VE, Con: ↑peak VO$_2$, ↑exercise time, ↑CP, ↑VT, ↔ VE, VE/VCO$_2$ slope, RER Between groups: Exp ↑Exercise time, ↑CP Vs Con ↔ peak VO$_2$, VE/VCO$_2$ slope, VT, VE, RER, peak VO$_2$		Exp: ↑Qol , ↓NYHA, ↑LVEF (%), ↑LVEDD, ↑LVESD ↔ dyspnea Con: ↑LVEF (%),↑LVESD ↔ Qol, LVEDD, NYHA, dyspnea Between groups: Exp ↑Qol, ↓dyspnea Vs Con ↔ NYHA, peak VO$_2$, LVEF (%), LVEDD, LVESD
Laoutaris et al,[16] 2011	15 CHF Exp= 10 Age: 37.2±17.7 yr Con= 5 Age: 41.8±14.6 yr	AT	IMT/AT	10 wk Both groups walked every day for 30-45 min Exp: Bike or treadmill I: moderate 12-14 of Borg scale T: 45 min F: 3-5x/wk IMT: I: 60% of SMIP F: 2-3x/wk		Exp: ↑MIP, ↑SMIP Con: ↔ MIP, SMIP Between groups: Exp ↔ MIP, SMIP Vs Con	Exp: ↑peak VO$_2$, ↑VO$_2$ at ventilatory threshold, ↑6MWT, ↓VE/VCO$_2$ slope ↔ VE, RER, exercise time Con: ↔ peak VO$_2$, VE/VCO$_2$ slope, VO$_2$ at ventilatory threshold,	Exp: ↑IC lung, ↔ FVC (%), FEV$_1$ (%), FEV$_1$/FVC Con: ↔ IC lung, FVC (%), FEV$_1$ (%), FEV$_1$/FVC Between groups: ↔ IC lung, FVC (%), FEV$_1$ (%), FEV$_1$/FVC	Exp: ↑Qol, ↔ dyspnea Con: ↔ Qol, dyspnea Between groups: ↔ dyspnea, Qol

							VE, RER, exercise time Between groups: ↔ 6MWT, peak VO_2, VO_2 at ventilatory threshold, VE/VCO_2 slope, VE, RER, exercise time		
Bosnak-Guclu et al,[17] 2011	30 CHF Exp= 16 Age: 69.50±7.96 yr Con= 14 Age: 65.71±10.52 yr NYHA: II-III	Sham-IMT	IMT	6 wk Exp: I: 40% of MIP adjusted weekly to maintain 40% of MIP Con: I: 15% of MIP T:30 min/d F: 7x/wk RR: 25-30 breaths at each workload	Exp: ↑balance, ↑QFMS, ↑QFMS (%) Con: ↔ QFMS, QFMS (%), balance Between groups: Exp ↑QFMS ↑balance Vs Con	Exp: ↑MIP, ↑MIP (%), ↑MEP, ↑MEP (%) Con: ↑MIP, ↑MIP (%), ↑MEP ↔ MEP (%) Between groups: Exp ↑MIP,↑MIP (%), ↑MEP Vs Con	Exp: ↑6MWT, 6MWT (%) Con: ↔ 6MWT Between groups: Exp ↑6MWT, 6MWT (%) Vs Con	Exp: ↑FVC (%), ↑FEV_1 (%), ↔ FEV_1/FVC Con: ↑FVC (%), ↔ FEV_1/FVC Between groups: Exp ↑FEV_1/FVC Vs Con ↔ FEV_1 (%), FVC(%)	Exp: ↓fatigue,↑Qol, ↓dyspnea, Con: ↑Qol ↔ dyspnea, fatigue Between groups: Exp ↓dyspnea Vs Con ↔ fatigue, Qol
Adamopoulos et al,[18] 2014	43 CHF Exp= 21 Age: 57.8 ± 11.7 yr Con= 22 Age: 58.3±13.2 yr NYHA: II-III	AT/SHAM-IMT	AT/IMT	12 wk F: 3x/wk AT for both groups: I: 70-80% max HR T: 45 min Exp: I: 60% of SMIP T:30 min		Exp: ↑SMIP, ↑MIP Con: ↑MIP, ↔SMIP Between groups: Exp: ↑SMIP, ↔ MIP Vs Con	Exp: ↑peak VO_2, ↑exercise time, ↑VE, ↑RER ↔ VE/VCO2 slope, VT, CP Con: ↑peak VO_2 ↔ VE/VCO_2 slope, VT, VE, RER,	Exp: ↔ FEV_1, FEV1/FVC, FVC Con: ↔ FEV_1, FEV_1/FVC, FVC Between groups: ↔ FEV_1, FEV_1/FVC, FVC	Exp: ↑Qol, ↑LVEF (%), ↓LVESD, ↓NYHA, ↓dyspnea ↔ LVEDD Con: ↑LVEF (%), ↓LVESD, ↓NYHA ↔ Qol, LVEDD, dyspnea Between groups:

				TIRE Protocol: 6 inspiratory efforts at each level: Level 1-60s R Level 2-45s R Level 3-30s R Level 4-15s R Level 5-10s R Level 6-5s R (to exhaustion) Con I: 10% of SMIP T: 30 min			exercise time, CP Between groups: ↔ VE/VCO_2 slope, VT, VE, RER, exercise time, CP, peak VO_2		Exp ↑Qol, ↓Dyspnea Vs Con ↔ LVEDD, LVESD, LVEF (%), NYHA
Moreno et al,[19] 2017	26 CHF Exp= 13 Age: 61±14 yr Con= 13 Age: 60±13 yr NYHA: II-III	Sham-IMT	IMT	8 wk F: 6x/wk T: 30min/d Exp: I: 30% of MIP RR: 15 breaths/min Con: I: 2% of MIP IMMP: IRT set at 60% of MIP for 1 min after ↑ to 70%, 80% and 90% of MIP until fatigue		Exp:↑MIP Con: ↔ MIP Between groups: IMT ↑ MIP Vs Con	Exp: ↑VO_2 Con: ↑VO_2 Between groups: ↔ VO_2		Exp:↑Qol Con: ↔ Qol Between groups: Exp ↑Qol Vs Con
Hossein Pour et al,[20] 2019	84 CHF Exp= 42 Age: 55.97±9.43 yr Con= 42 Age: 57.28±9.06 yr NYHA: II-III/IV	Sham-IMT	IMT	6 wk F: 1x/d, 7d/wk T: 30 min, 3 min sets of training R: 1 min/set Exp: I: 40% of MIP					Exp: ↓NYHA, ↓dyspnea Con: ↑dyspnea, ↔ NYHA Between groups: Exp ↓dyspnea, fatigue, NYHA Vs Con

				Training load adjusted to maintain 40% of MIP weekly Con: I: 10% of MIP					
Mello et al,[21] 2012	27 CHF Exp= 15 Age: 54.3 ±2 yr Con= 12 Age: 53.3 ±2 yr	No intervention	IMT	12 wk F: 3x/d, 7x/wk T: 10 min Exp: I: 30% of MIP Con: no inspiratory load	Exp: ↑MSNA Con:↔ MSNA Between groups: Exp ↔ MSNA Vs Con	Exp: ↑MIP Con ↔ MIP Between groups: Exp ↑MIP Vs Con	Exp: ↑peak VO_2, ↓VE/VCO_2 peak ↓VE/VCO_2 slope Con ↔ peak VO_2, VE/VCO_2 slope, VE/VCO_2 peak Between groups: Exp ↑peak VO_2, ↓VE/VCO_2 peak, ↓VE/VCO_2 slope Vs Con		Exp: ↑Qol Con: ↔ Qol Between groups: Exp ↑Qol Vs Con
Hornikx et al,[22] 2020	20 CHF Exp=10 Age: 64±8 yr Con=10 Age: 58±11 yr	AT/RT	RHIIT (RT/HIIT/IRT)	12 wk F: 3x/wk Con: I: 50% Wpeak (3 min warm up, 2x7 min cycling, 2x7 min walking in treadmill, 12 min: rowing, step and armergometry) RT: callis-	Exp: ↑QFMS Con: ↔QFMS Between groups: Exp ↑QFMS Vs Con	Exp: ↑MIP Con: ↔ MIP Between groups: Exp ↑MIP Vs Con	Exp: ↑peak VO_2, ↔ VE/VCO_2 Con: ↑VO_2 peak, ↔ VE/VCO_2 Between groups: ↔ peak VO_2, VE/VCO_2		Exp: ↑Qol Con: ↔ Qol Between groups: ↔ Qol

				thenics exercises (20 min) Exp: HIIT: cycling I: 80% of Wpeak T: 33 min RT: I: 65 % of 1RM (2 set/10 rep on a leg press) IRT: F: 2x/d I:50% of MIP RR: breath in & out 30 times					
Chen et al,[23] 2016	21 CHF Exp= 11 Age: 63.73 ±14.64 yr Con= 10 Age: 67.50± 10.35 yr	Stroke rehabilitation program	IMT	10 wk F: 1x/d, at least 5x/wk T:30 min Exp: I: 30%of MIP with ↑ 2cmH_2O each wk Exp+Con: participated in a conventional stroke rehabilitation program Con: did not receive any IMT		Exp: ↑MIP, ↔ MEP Con: ↔ MIP, MEP Between groups: Exp ↑MIP, ↔ MEP Vs Con		Exp: ↑FVC, ↑FEV_1, ↔ FEV_1/FVC Con: ↔ FEV_1, FEV_1/FVC Between groups: ↔ FEV1, FVC, FEV_1/FVC	
Kawauchi et al,[24] 2017	35 CHF Exp1= 13Age: 54±10 yr Exp2= 13 Age: 56±7 yr	No intervention	Exp$_1$= LIPRT (IMT/RT) Exp$_2$= MIPRT	8 wk F: 7d/wk LIPRT: IMT: I: 15% of MIP RT: 0.5 kg (upper & lower limbs	Exp$_1$: ↑Quadriceps strength Exp$_{1,2}$: ↑Quadriceps strength	Exp$_1$: ↑MEP, ↑MIP Exp$_2$: ↑MIP, ↑MEP Con: ↔ MIP, MEP	Exp$_1$: ↑6MWT Exp$_2$: ↑6MWT Con: ↔ 6MWT	Within & Between groups: ↔ FEV_1 (%), FVC (%), FEV_1/FVC	Exp$_1$: ↑Qol, ↔ NYHA Exp$_2$: ↑Qol, ↓NYHA Con: ↑Qol, ↔NYHA

	Con= 9 Age: 56±7 yr NYHA: II/III		(IMT/RT)	exercises), 10 rep/exercise during first 2 wk, 2set/10 rep for the remaining 6 wk MIPRT: IMT: I: 30% of MIP RT: 50% of 1RM	(1RM) Vs Con	Between groups: Exp_1 $\uparrow$MIP, $\leftrightarrow$ MEP Vs Con Exp_2 $\uparrow$MIP, $\uparrow$MEP Vs Con	Between groups: $Exp_{1,2}$ $\uparrow$6MWT Vs Con		Between groups: $\leftrightarrow$ Qol, NYHA
Antunes-Correa et al,[25] 2020	33 CHF Exp1= 11 Age: 55±3 yr Exp2= 12 Age: 57±2 yr Con= 10 Age: 57±3 yr NYHA: II-III	No intervention	Exp_1= IMT Exp_2= AT	4 mo Exp_1: I: 60% of MIP F: 5x/wk T: 30 min RR: 15-20 breaths/min Exp_2: F: 3x/week Each session included: 5 min stretching exercises, 40 min of cycling, 10 min strengthening exercises R: 5 min		Exp_1: $\uparrow$MIP Exp_2: $\leftrightarrow$ MIP Con: $\leftrightarrow$ MIP Between groups: Exp_1 $\uparrow$MIP Vs Con Exp_2 $\leftrightarrow$ MIP Vs Con	Exp_1: $\uparrow$peak VO_2, $\uparrow$peak workload Exp_2: $\uparrow$peak VO_2, $\uparrow$peak workload Con: $\uparrow$peak workload, $\leftrightarrow$ peak VO_2 Between groups: $Exp_{1,2}$ $\uparrow VO_2$ peak Vs Con Exp $_2$ $\uparrow$peak workload Vs Con Exp_1 $\leftrightarrow$ peak workloadVs Con		Exp_1: $\uparrow$Qol Exp_2: $\uparrow$Qol Con: $\uparrow$Qol Between groups: $Exp_{1,2}$ $\uparrow$Qol Vs Con
Palau et al,[26] 2014	26 CHF (HFpEF) Exp= 14Age: 68 (60–76) y	Usual care	IMT +Usual care	12 wk F: 2x/d T: 20 min Exp: I: 25-30% of MIP		Exp: $\uparrow$ MIP Between: Exp: $\uparrow$MIP Vs Con	Exp: $\uparrow$peak VO_2, $\uparrow VO_2$ AT, $\downarrow VE/VCO_2$ slope, $\uparrow$RER, $\uparrow$6MWT		Exp: $\uparrow$Qol, $\leftrightarrow$ LVEF (%) Con $\leftrightarrow$ LVEF (%), Qol Between groups: Exp

	Con= 12Age: 74 (73–77) yr NYHA: III/IV						Con ↔ VE/VCO_2 slope, VO_2 AT, ↓peak VO_2, 6MWT Between groups: Exp ↑peak VO_2, ↑VO_2 AT, VE/VCO_2 slope ↑ 6MWT, ↑RER Vs Con		↑Qol Vs Con, ↔ LVEF (%)
Palau et al,[27] 2019	59 (HFpEF) Con= 13 Exp1= 15 Exp2= 15 Exp3= 16 Age: 74±9 yr NYHA: II-III/IV	Usual care	Exp_1: IMT (home based) Exp_2: FES Exp_3: IMT +FES	12 wk & 6 mo follow up Exp_1: F: 2x/d T: 20 min/session I: 25% to 30% of their MIP Exp_2: FES program for both legs T: 45 min F: 2d/wk for a total of 12 wk Stimulator: F: 10 to 50Hz, for 5s R: 5s Exp3: re-ceived IMT and FES training at the same time			Exp_1: ↑peak VO_2 (3 & 6 mo) ↓VE/VCO_2 slope (6 mo) ↑6MWT (3 & 6 mo), ↔ VE/VCO_2 slope (3 mo) Exp_2: ↑peak VO_2 (3 & 6 mo) ↑6MWT (3 & 6 mo), ↔ VE/VCO_2 slope (3 & 6 mo) Exp_3: ↑peak VO_2 (3 & 6 mo) ↓VE/VCO_2 slope (3 mo), ↑6MWT (3 & 6 mo), ↔ VE/VCO_2		Exp_1: ↑QoL (3 & 6 mo) Exp_2: ↑Qol (3 mo), ↔ Qol (6 mo) Exp_3 : ↑Qol (3 & 6 mo) Between groups: $Exp_{1,2,3}$ groups ↑ Qol (3 mo) Vs Con ↔ LVEF (%), LVEDD, LVESD

							slope (6 mo) Between groups: $Exp_{1,2,3}$ groups ↑peak VO_2 (3 & 6 mo) Vs Con $Exp_{1,2,3}$ groups ↑6MWT (3 mo) Vs Con, at 6 mo this beneficial effects persisted for $Exp_{2,3}$ ↔ peak VO_2, VE/VCO_2 slope between $Exp_{1,2,3}$ groups		
Ekman et al,[28] 2011	65 CHF Exp= 30 Con= 35 Age: 73±11 yr NYHA: II-IV	Music listening	DGB	4 wk Exp: DGB exercises F: 2x/d T: 20 min/session RR: <10 breaths/min Con: listened music					Exp: ↓dyspnea, ↓NYHA Con: ↔ dyspnea, NYHA Responders in Exp (an average increase in Tex/Tin of >0.2 and a reduction in the average respiration rate): ↓breathlessness, ↓NYHA compared with no-responders or controls Between groups ↔

									dyspnea, NYHA
Drozdz et al,[29] 2016	40 CHF Exp1= 20 Exp2= 20 Age: 63.3 ± 13.4 yr NYHA: II-III	Usual care	DGB	Exp_1: started with 10-12 wk SBT followed by 10-12 wk usual care Exp_2: started with 10-12 wk usual care followed by 10-12 wk SBT SBT: F: 2x/d T: 15 min/session RR: 6 breaths/min					Exp1: ↑Qol Exp2:↔ Qol Between groups ↔ Qol
Seo et al,[30] 2015	36 CHF Exp=18 Age: 65.2±11.34 yr Con= 18 Age: 66.6±13.69 yr NYHA: II-IV	Attention group	DBR	8 wk & 5 mo follow up Exp: received 3 audio CDs (1 each for wk 1, wk 2, & wk 3-8) RR: 6 breaths/min F: 2x/day at least 5 d/wk Week 1 goal: 5 min of CD-guided DBR Week 2 goal: 10 min of CD-guided DBR Weeks 3-8 goal: 15 min of CD-guided DBR + 4 telephone calls (feedback & encourage)			Exp: ↑6MWT (8 wk & sustained at 5 mo follow up) Con:↑6MWT (8 wk) Between groups: ↔ 6MWT (8 weeks & 5 mo)		Exp & Con: ↓dyspnea (8 wk & 5 mo) Between groups: ↔ dyspnea (8 weeks & 5 mo)

				Con: received 4 telephone calls with general health topics					
Kawecka-Jaszcz et al,[31] 2017	96 CHF Age: 64.5 (57.0–71.5) yr NYHA: I-III	Usual care	DGB	Exp_1: started with 10-12 wk SBT followed by 10-12 wk usual care Exp_2: started with 10-12 wk usual care followed by 10-12 wk SBT SBT: F: 2 x/day T: 15 min/session RR: 6 breaths/min			After SBT: ↑6MWT		After SBT: ↑EF, ↑LVEF (%), ↓LVEDD
Lachowska et al,[32] 2019	21 HFrEF Exp= 11 Con= 10Age: 52±17 yr NYHA: I-III		DGB	12 wk & 6 mo follow up SBT: F: 2x/d T: 15 min/session (totally 30 min) RR: 10 breaths/ min At 3 mo follow up-$Group_1$: continue SBT $Group_2$: no SBT			SLOWB from baseline to 6 mo follow up: ↑6MWT & peak RER in Group 1 but no Group 2 ↔ peak VO_2, VE/VCO_2 from baseline to 3 mo follow up		SLOWB: ↔ LVEF (%), LVEDD (3 & 6 mo)

Abbreviations:

Exp: experimental, **Con:** control, **IMT:** inspiratory muscle training, **SBT:** slow breathing training, **DGB:** device-guided breathing, **IMMP:** inspiratory muscle metaboreflex protocol, **LVEF:** left ventricular ejection fraction, **LVESD:** left ventricular end-systolic diameter, **LVEDD:** left ventricular end-diastolic diameter, **HR:** heart rate, **I:** intensity, **R:** rest, **F:** frequency, **T:** time, **RR:** respiratory rate, **MSNA:** muscle sympathetic nerve activity, **LIPRT:** low intensity inspiratory and peripheral resistance training, **RT:** resistance training, **IRT:** inspiratory resistance training, **HIIT:** high intensity interval training, **MIPRT:** moderate-intensity inspiratory and peripheral resistance training, **FES:** functional electrical stimulation **AT:** aerobic training, **DBR:** diaphragmatic breathing retraining, **RER:** respiratory exchange ratio, **SMIP:** sustained maximal inspiratory pressure, **MEP:** maximal expiratory pressure, **FEV_1:** forced expiratory volume in 1 s, **FVC:** forced vital capacity**, QFMS:** quadriceps femoris muscle strength, **QMT:** quadriceps muscle torque, **QME:** quadriceps muscle endurance, **CP:** circulatory power, **VT:** ventilatory threshold, **VE:** minute ventilation, **TG:** training group, **IC:** inspiratory capacity, **EF:** ejection fraction, **peak VO_2:** peak oxygen consumption, **VE/VCO_2:** ventilation/carbon dioxide, **6MWT:** 6 min walk test, **1RM**: 1 repetition maximum, **Rep:** repetition, **NYHA:** New York Heart Association, **Qol:** quality of life, **↔:** no changes, **↑:** increased, **↓:** reduced, **%:** predicted