

Current insights of inspiratory muscle training on the cardiovascular system: a systematic review with meta-analysis

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Background: Cardiorespiratory limitation is a common hallmark of cardiovascular disease which is a key component of pharmacological and exercise treatments. More recently, inspiratory muscle training (IMT) is becoming an effective complementary treatment with positive effects on muscle strength and exercise capacity. We assessed the effectiveness of IMT on the cardiovascular system through autonomic function modulation via heart rate variability and arterial blood pressure.

Methods: Randomized controlled trials (RCTs) were identified from searches of The Cochrane Library, MEDLINE and EMBASE to November 2018. Citations, conference proceedings and previous reviews were included without population restriction, comparing IMT intervention to no treatment, placebo or active control.

Results: We identified 10 RCTs involving 267 subjects (mean age range 51–71 years). IMT programs targeted maximum inspiratory pressure (MIP) and cardiovascular outcomes, using low ($n=6$) and moderate to high intensity ($n=4$) protocols, but the protocols varied considerably (duration: 1–12 weeks, frequency: 3–14 times/week, time: 10–30 mins). An overall increase of the MIP (cmH₂O) was observed (-27.57 95% CI -18.48 , -37.45 , $I^2=64\%$), according to weighted mean difference (95%CI), and was accompanied by a reduction of the low to high frequency ratio (-0.72 95% CI -1.40 , -0.05 , $I^2=50\%$). In a subgroup analysis, low- and moderate-intensity IMT treatment was associated with a reduction of the heart rate (HR) (-7.59 95% CI -13.96 , -1.22 bpm, $I^2=0\%$) and diastolic blood pressure (DBP) (-8.29 [-11.64 , -4.94 mmHg], $I^2=0\%$), respectively.

Conclusion: IMT is an effective treatment for inspiratory muscle weakness in several populations and could be considered as a complementary treatment to improve the cardiovascular system, mainly HR and DBP. Further research is required to better understand the above findings.

Keywords: breathing exercises, respiratory muscle training, cardiovascular system

Introduction

Inspiratory muscle weakness may induce several impairments in both healthy^{1,2} and athletic individuals.^{3,4} Similarly, studies have demonstrated that inspiratory muscle strength also has an important role in the pathophysiology of exercise limitation in several clinical conditions.⁵ More recently, studies have found that maximal inspiratory pressure (MIP) is strongly correlated with VO₂peak in patients after acute myocardial infarction and heart failure,⁶ reinforcing the influence of the inspiratory muscles on functional capacity.

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Furthermore, studies suggest that inspiratory muscle strength may influence central hemodynamic measurements at rest, including cardiac output, mean arterial pressure and vascular resistance in heart failure patients.⁷ In this sense, inspiratory muscle training (IMT) has been tested to evaluate its effect over the autonomic nervous activity and blood pressure control.^{8–10} Ferreira et al⁹ demonstrated a significant influence of IMT on 24-hrs ambulatory blood pressure monitoring by reducing systolic and diastolic blood pressure (SDP and DBP) 7.9 and 5.5 mmHg, respectively.

More recently, IMT has been evaluated as an adjunct therapy to improve autonomic modulation due to the recognized respiratory effects. According to several studies, IMT may reduce sympathetic activity^{9,11} through respiratory muscle metaboreflex attenuation,¹² improving functional capacity and physical performance.^{12–15} Therefore, the purpose of this study was to systematically review the effects of the IMT on global cardiovascular function through autonomic function modulation of heart rate variability (HRV) and arterial blood pressure.

Methods

This systematic review with meta-analysis was conducted following the PRISMA Statement for Reporting Systematic Review Analysis.¹⁶

Criteria for considering studies for this review

Type of studies

Controlled clinical trial studies evaluating IMT effects on cardiovascular function were included in the systematic review.

Types of participants

The trials evaluating IMT effects on blood pressure and autonomic modulation, without population restriction. The eligibility criteria to select studies were: i) the primary objective was related to the effects of IMT on the cardiovascular autonomic nervous system, arterial blood pressure and heart rate (HR), and ii) randomized clinical trials. Exclusion criteria were non-randomized trials and articles addressing other breathing exercises modalities (yoga, slow and fast breathing, expiratory muscle training).

Types of intervention

We included studies examining a program of IMT (≥ 1 week treatment) offered as a sole intervention or as an adjuvant to

another form of exercise. Interventions could be compared to either an inactive control (eg, no treatment, placebo, or sham NMES) or an active control such as an alternative form of exercise. A placebo intervention was defined as a treatment group in which an identical IMT, but without resistance or with minimum resistance. A control intervention was defined as either no treatment (non-active) or another treatment modality (active control) not including IMT protocol.

Types of outcome

The primary outcomes were HR (measured by beats per minute, bpm), SBP, DBP and mean blood pressure (measured by millimeters of mercury, mmHg) and HRV frequency domain components (LF, HF, and LF/HF; measured in normalized units). Inspiratory muscle strength (MIP; measured by cmH₂O).

Search method for identification of studies

The Cochrane Library (online version 2018), PUBMED (1962–2018), EMBASE (1980–2018) electronic databases were searched to identify eligible studies. Two reviewers analyzed the results independently (GRC and GCJ). Searches were limited to randomized, controlled trials (RCTs) and a filter was applied to limit the search to human trials. No language restrictions were included. A sensitive search strategy for identifying RCTs was employed [16]. Additional studies were identified from the reference lists of the retrieved studies.

Keywords employed during searches

“Breathing Exercises“[Mesh] OR “Maximal Respiratory Pressures“[Mesh] OR “Respiratory Muscles“[Mesh] OR “Muscle Strength“[Mesh]) AND (“Blood Pressure“[Mesh] OR “Arterial Pressure“[Mesh] OR “Baroreflex“[Mesh] OR “Heart Rate“[Mesh] OR “Blood Pressure Monitoring, Ambulatory” OR “Autonomic Nervous System”[Mesh] OR “Vascular Resistance”[Mesh] OR “Sympathetic Nervous System”[Mesh]) AND ((Clinical Study[ptyp] OR Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Controlled Clinical Trial [ptyp] OR Pragmatic Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp] OR Research Support, American Recovery and Reinvestment Act[ptyp] OR Research Support, N I H, Extramural[ptyp] OR Research Support, N I H, Intramural[ptyp] OR Research Support, Non U S Gov’t [ptyp] OR Research Support, U S Gov’t, Non P H S[ptyp] OR Research Support, U S Gov’t, P H S[ptyp] OR Research Support, US Government[ptyp]) AND Humans[Mesh]

Data collection and analysis

Study selection

The articles retrieved during the searches were initially screened based on the title and abstract for the exclusion of clearly irrelevant studies. For selection, abstracts had to identify the study design, appropriate population and relevant components of the intervention, as described above. Full-text articles of all potentially relevant RCTs were obtained and assessed independently by two reviewers (GRC and GCJ) for eligibility based on the defined inclusion criteria.

Quality assessment

The risk of bias in the eligible RCTs was assessed by a single reviewer (FVSC) and verified by a second reviewer (GRC). The following aspects of methodological quality were assessed: concealment of the allocation, intention-to-treat analysis, outcome assessment blinding and description of losses and exclusions. Quality was also evaluated globally using the scale proposed by PEDro scale.¹⁷

Data extraction

Relevant data regarding inclusion criteria (study design, participants, duration, frequency, intensity, comparisons, and outcomes), the risk of bias (randomization, blinding, attrition, and control) and results were extracted. If the study had more than two groups, we included those that presented with the greater effect size. Data extraction was performed by a single reviewer (GRC) and checked by a second reviewer (GCJ). Disagreements were resolved by consensus. The agreement ratio before amending any discrepancies was assessed using the Kappa coefficient, which was higher than 0.90. Authors were contacted when necessary for clarifications or to obtain further outcome details.

Statistical analysis

The data were processed following the Cochrane Handbook for Systematic Reviews of Interventions. For continuous variables, net changes were compared (ie, IMT group vs control group) by the weighted mean difference (WMD) and 95% CI. The SD was calculated for each study based on the change score method. Heterogeneity among the studies was explored qualitatively by comparing the characteristics of the studies and quantitatively using the chi-squared test of heterogeneity and the I^2 statistic. When appropriate, the results of the studies were combined for each outcome to determine the overall estimate of the treatment effect. The effect model for meta-analysis was elected based on

qualitative and quantitative analyses as well as the analysis of publication bias. All analyses were conducted using Review Manager version 5.3.

Results

Identification and selection of studies

The initial search led to the identification of 975 studies, among which 855 were considered potentially relevant based on the title and abstract. Twenty-nine potentially relevant studies were retrieved for detailed analysis.^{8,11,18–34} Only 10 articles met the eligibility criteria.^{9,35–43} Figure 1 shows the flowchart of the study selection process. Excluded studies and the reasons for their exclusion are detailed in Table 1.

Description of studies and participants

The 10 studies analyzed involved a total of 267 subjects. Descriptions of all studies are presented in Table 2.

Interventions characteristics

The most common IMT intensity was low-intensity. Six studies compared the effects of low-intensity IMT,^{9,35,36,38,40,43} two studies examined moderate intensity

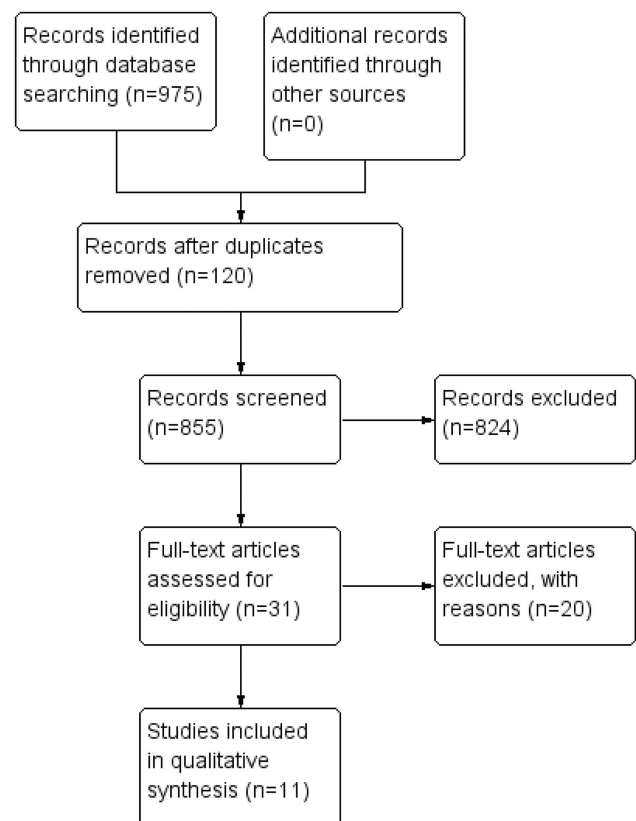


Figure 1 Study flow diagram.

Table 1 Characteristics of the excluded studies

Study	Reason for exclusion
Souza et al ¹⁸	Non-randomized trial and
Jones et al ¹⁹	Other breathing exercise
Posser et al ⁸	Protocol study
Drozdz et al ²⁰	Other breathing exercise
Gething et al ²¹	Comparison between intensities different
Jaenisch et al ³⁰	Animal study
Laohachai et al ²³	Non-randomized study and without control group
Kaminski et al ¹¹	Absence of baseline and post-intervention data
Laoutaris et al ²⁴	Non-randomized study and without control group
Logtenberg et al ²⁵	Other breathing exercise
Mourya et al ²⁶	Other breathing exercise
Tong et al ²⁷	Inspiratory muscle training plus functional exercise
Passfield et al ²⁸	Hyperpnea during respiratory muscle training and without outcomes
Correa et al ²⁹	Heart rate, systolic and diastolic blood pressure were not shown
Jaenisch et al ²²	Animal study
Sangthong et al ³¹	Other breathing exercise
Silva et al ³⁴	Data without mean
Vivodtzev et al ³²	Mixed intervention
Ditterline et al ³³	Absence of baseline and post-intervention data

IMT^{39,41} and two studies examined high-intensity IMT.^{37,42} Four studies used a medium resistance spring load device (PowerBreathe Classic, PoweBreathe International Ltd., Warwickshire, England, UK) to produce IMT,^{39–42} five studies used another spring-loaded device (Threshold IMT, Philips, Rotterdam, Netherlands)^{9,36,38,39,43} and one used another form of IMT (Threshold PEP, Philips).³⁵ The studies were quite heterogeneous, and Table 3 provides a summary of the interventions employed in the different studies.

Quality of the studies

The methodological quality of the eligible RCTs is presented in Table 3. The quality of most studies was poor to good. According to PEDro scale, six studies reached 4 to 5 points and four studies 6 to 7 points.

Effect of IMT on inspiratory muscle strength

The most frequent training intensity used was 30% of the MIP defined as low-intensity and four studies used 50% of the MIP (moderate-high intensity).⁴⁴ Treatment duration

Table 2 Demographics and clinical characteristics of the included studies

Study	Description		IMT group description		Comparison group	
	Study design	Population	n	Age (years)	n	Age (years)
Campos et al (2018) ³⁵	RCT	Chronic kidney disease	41	48.8±12.9	12	52.67±14.6
Rodrigues et al (2018) ⁴¹	RCT	Older healthy	20	64±3.0	8	64±4.0
DeLucia et al (2018) ³⁷	RCT	Healthy women	28	21.2±5.5	13	19.6±6.1
Ferreira et al (2017) ⁹	RCT	Hypertensive	13	61.8±4.0	7	52.1±8.8
Feriani et al (2017) ⁴³	CT	Metabolic Syndrome	28	69±4.0	12	68±3.0
Moreno et al (2017) ⁴⁰	RCT	Chronic heart failure	26	61±14	13	60±13.0
Vranish et al (2016) ⁴²	RCT	Obstructive sleep apnea	24	61±13.5	12	69.1±11.7
Mills et al (2015) ³⁹	RCT	Older healthy	34	69±3.0	17	68±3.0
Mello et al (2012) ³⁸	RCT	Chronic heart failure	28	54.3±7.7	13	53.3±7.2
Correa et al (2011) ³⁶	RCT	Diabetes	25	63±7.0	13	63±7.0

Note: Age expressed in mean ± SD.

Abbreviations: CT, clinical trial; RCT, randomized clinical trial; IMT, inspiratory muscle training.

Table 3 Intervention description of the included studies

Study	IMT group description						Comparison group	Score PEDro
	Intensity (MIP)	Frequency (day/week)	Duration (week)	Time	Intensity type	Training type	Description	
Campos et al (2018) ³⁴	15 cmH ₂ O 20 cmH ₂ O	3	8	30 mins	Low	Resistor Threshold PEP	Control	6/10
Rodrigues et al (2018) ⁴⁰	30% (1 week) 50% after	2×day/5–7 days	5	30 breaths	Moderate	Resistor PowerBreathe Classic	Control	4/10
DeLucia et al (2018) ³⁶	75%	5	6	–	High	Resistor Pressure Transducer	Sham (15% PImax)	7/10
Moreno et al (2017) ³⁹	30%	6	8	30 mins	Low	Resistor Threshold IMT and Powerbreathe	Control	5/10
Feriani et al (2017) ⁴²	30%	3 sets	1	15 mins	Low	Resistor Threshold IMT	Control	5/10
Vranish et al (2016) ⁴¹	75%	Twice/day	6	30 breaths	High	Resistor PowerBreathe Classic	Sham (15% PImax)	5/10
Mills et al (2015) ³⁸	50%	7	8	30 breaths	Low	Resistor PowerBreathe Classic	Control	5/10
Ferreira et al (2013) ⁹	30%	7	8	30 mins	Low	Resistor Threshold IMT	Control	6/10
Mello et al (2012) ³⁷	30%	3×day during 7 week	12	10 mins	Low	Resistor Threshold IMT	Control	4/10
Correa et al (2011) ³⁵	30%	7	8	30 mins	Low	Resistor Threshold IMT	Control	6/10

Abbreviations: PEP, positive expiratory pressure; IMT, inspiratory muscle training; MIP, maximal inspiratory pressure.

ranged from 1 to 12 weeks. All protocols performed weekly readjustments of MIP (Table 3). The number of training sessions ranged from 2 to 7 sessions per week for 15–30 mins duration. Three studies were performed twice or more per day.^{38,41,42} Six studies set the workload at 30% MIP with a total of 113 subjects in the IMT and 89 in the control group, and 4 studies which set the workload $\geq 50\%$ MIP with a total of 32 subjects in the IMT and 31 in the control group. Overall, IMT was associated with a significant improvement in MIP when data of all studies were pooled (10 studies, $n=263$ subjects, WMD=27.57 cmH₂O, 95% CI 18.48–37.45 cmH₂O, $I^2=64\%$) (Figure 2). From subgroup analysis, low-intensity and moderate-high intensity IMT protocols produced similar effects from both low and high intensity protocols (low intensity: 7 studies, $n=202$ subjects; WMD=28.42, 95% CI 12.37–44.46 cmH₂O, $I^2=73\%$; moderate-high intensity, 3

studies, $n=63$ subjects; WMD=25.55, 95% CI 19.42–31.68 cmH₂O, $I^2=73\%$).

Effect of IMT on hemodynamic measures Heart rate

Overall, IMT did not influence HR when data of all studies were pooled (10 studies, $n=152$ subjects, WMD=-4.32 bpm, 95% CI -9.56 to 0.91 bpm, $I^2=0\%$) (Figure 3A). In a subgroup analysis, only low-intensity IMT studies were associated with a reduction of the resting HR (4 studies, $n=108$ subjects; WMD=-7.59 bpm, 95% CI -13.96 to -1.22 bpm, $I^2=0\%$).

Systolic blood pressure

IMT did not modify SBP in the overall analysis (05 studies, $n=63$, WMD=-8.13 mmHg, 95% CI -21.17 to 4.91 mmHg, $I^2=89\%$). Subgroup analysis also did not

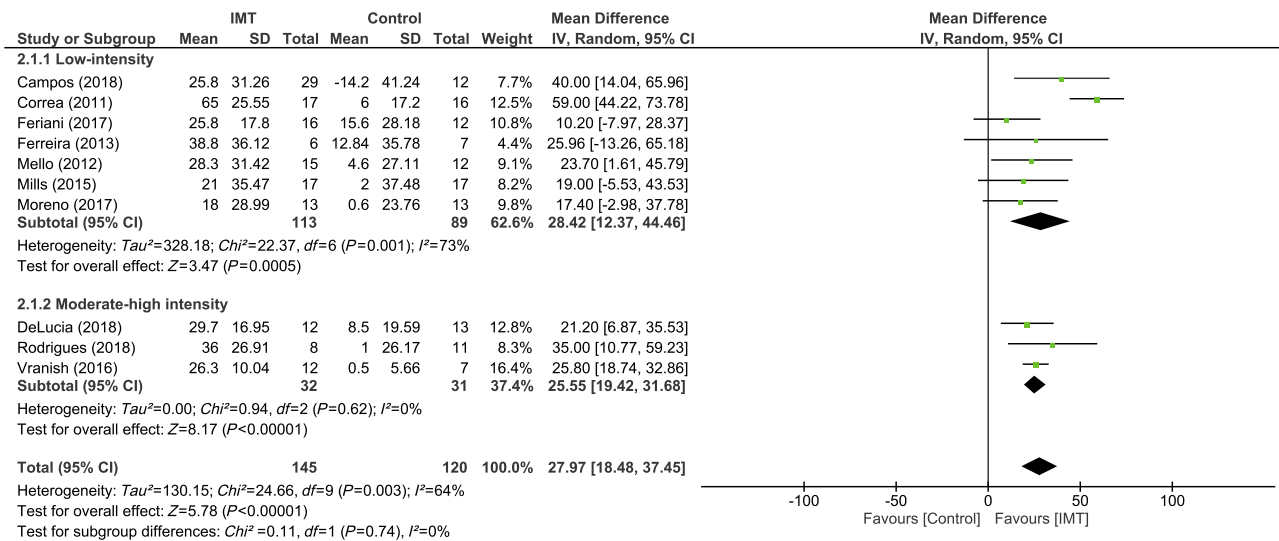


Figure 2 Forest plot depicts of inspiratory muscle training on inspiratory muscle strength compared to low and moderate-high intensity.

demonstrate effects either in low and moderate to high intensity protocols–low intensity (03 studies, $n=71$ subjects, $WMD=-0.94$ mmHg, 95% CI -10.53 to 8.66 mmHg, $I^2=0%$) and moderate-high intensity (02 studies, $n=44$, $WMD=-15.79$ mmHg, 95% CI -33.77 to 2.19 mmHg, $I^2=89%$) (Figure 3B).

Diastolic blood pressure

Overall, IMT was not associated with a significant reduction of the DBP when data of all studies were pooled (05 studies, $n=119$ subjects, $WMD=-3.30$ mmHg, 95% CI -9.63 to 3.04 mmHg, $I^2=76%$) (Figure 3C). Subgroup analysis found no positive effect of low-intensity IMT on DBP (03 studies, $n=75$ subjects; $WMD=2.12$ mmHg, 95% CI -1.78 to 6.01 mmHg, $I^2=0%$), but moderate-high intensity IMT was associated with a significant reduction in DBP (02 studies, $n=44$ subjects; $WMD=-8.29$ mmHg, 95% CI -11.64 to -4.94 mmHg, $I^2=0%$).

Effect of IMT on heart rate variability measures

Low- and high-frequency component

Overall analyses found that IMT did not favorably modulate the low- and high-frequency HRV components (Figure 4A and B). Subgroup analysis also found that low- and moderate-high intensity IMT was not associated with modulation of the low- and high-frequency HRV components.

Low- to high-frequency ratio

IMT was found to produce a slight reduction of the low- to high-frequency ratio when data of all studies were pooled

(06 studies, $n=144$ subjects, $WMD=-0.72$, 95% CI -1.40 to -0.05 , $I^2=50%$) (Figure 4C). From subgroup analysis, only one IMT study with moderate-high intensity produced a significant reduction in the low- to high-frequency ratio (01 study, $n=19$ subjects, $WMD=-2.29$, 95% CI -4.12 to -0.46 , $I^2=not applicable$).

Discussion

Despite the considerable heterogeneity of the IMT protocols which evaluated cardiovascular effects ($I^2>60%$), the results reaffirmed in both general or subgroup analysis an important effect of IMT on MIP with an overall effect of 27.57 cmH₂O (95% CI $18.48-37.45$). Regarding the cardiovascular effect of the IMT, this review only found a small decrease in the low to high-frequency ratio following IMT treatment -0.72 (95% CI -1.40 to -0.05). Moreover, from subgroup analysis, low-intensity IMT protocols were associated with an important reduction of the rest HR -7.59 bpm (95% CI -13.96 to -1.22) while moderate-high intensity protocols demonstrate a significant reduction in DBP -8.29 mmHg (95% CI -11.64 to -4.94) and greater effect on the low- to high-frequency ratio compared to the overall analysis 2.29 (95% CI -4.12 to -0.46). The effect from IMT on SBP in both overall and subgroup analysis (low and moderate-high intensity protocol) was not significant.

Selected studies on this meta-analysis included several different populations, including cardiovascular conditions (6 studies), healthy older adults (2 studies), Chronic kidney disease. (1 study), and obstructive sleep apnea (1 study).

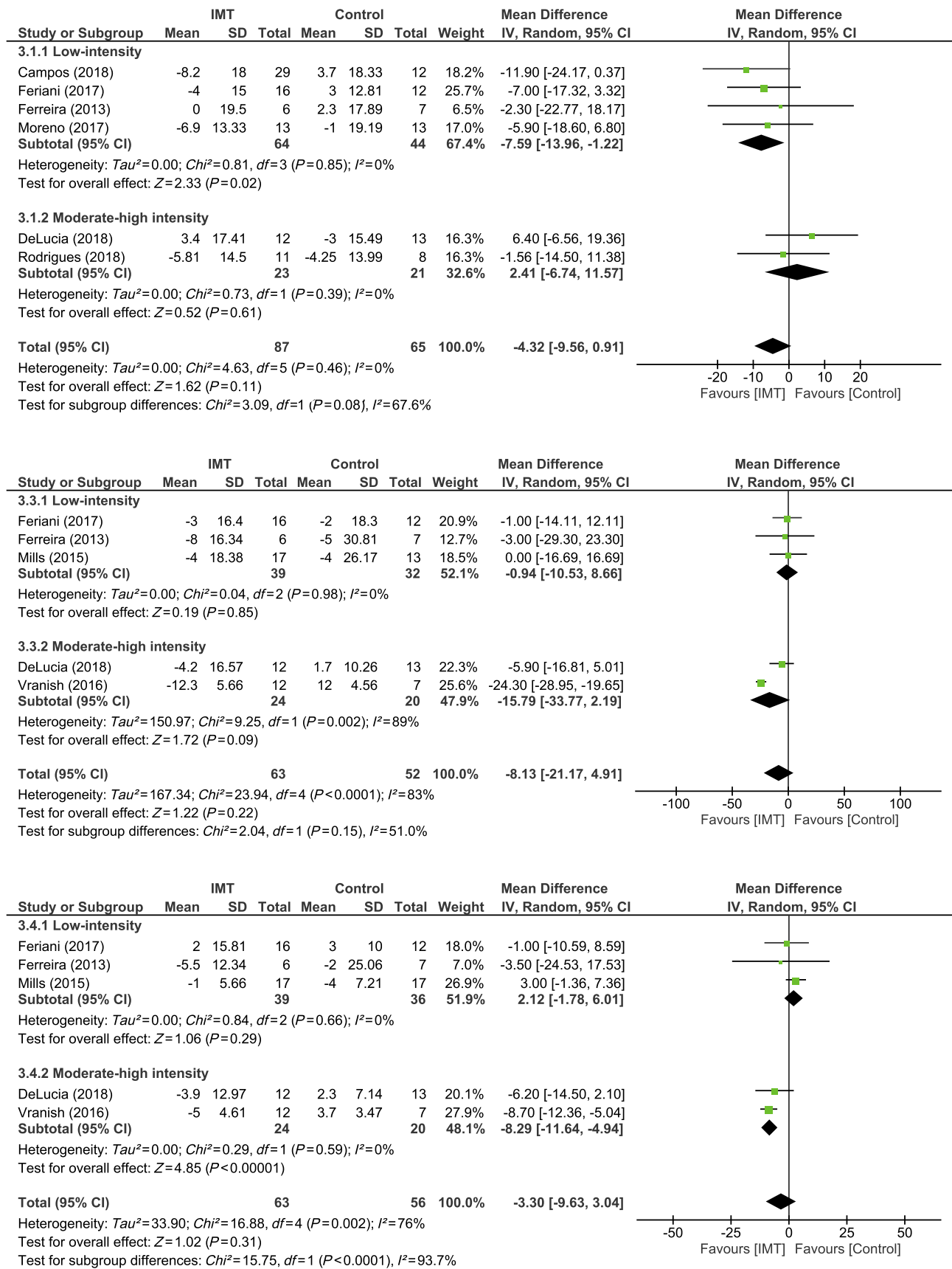


Figure 3 Forest plot depicts of inspiratory muscle training on (A) systolic blood pressure, (B) diastolic blood pressure, and (C) heart rate compared to low and moderate-high intensity.

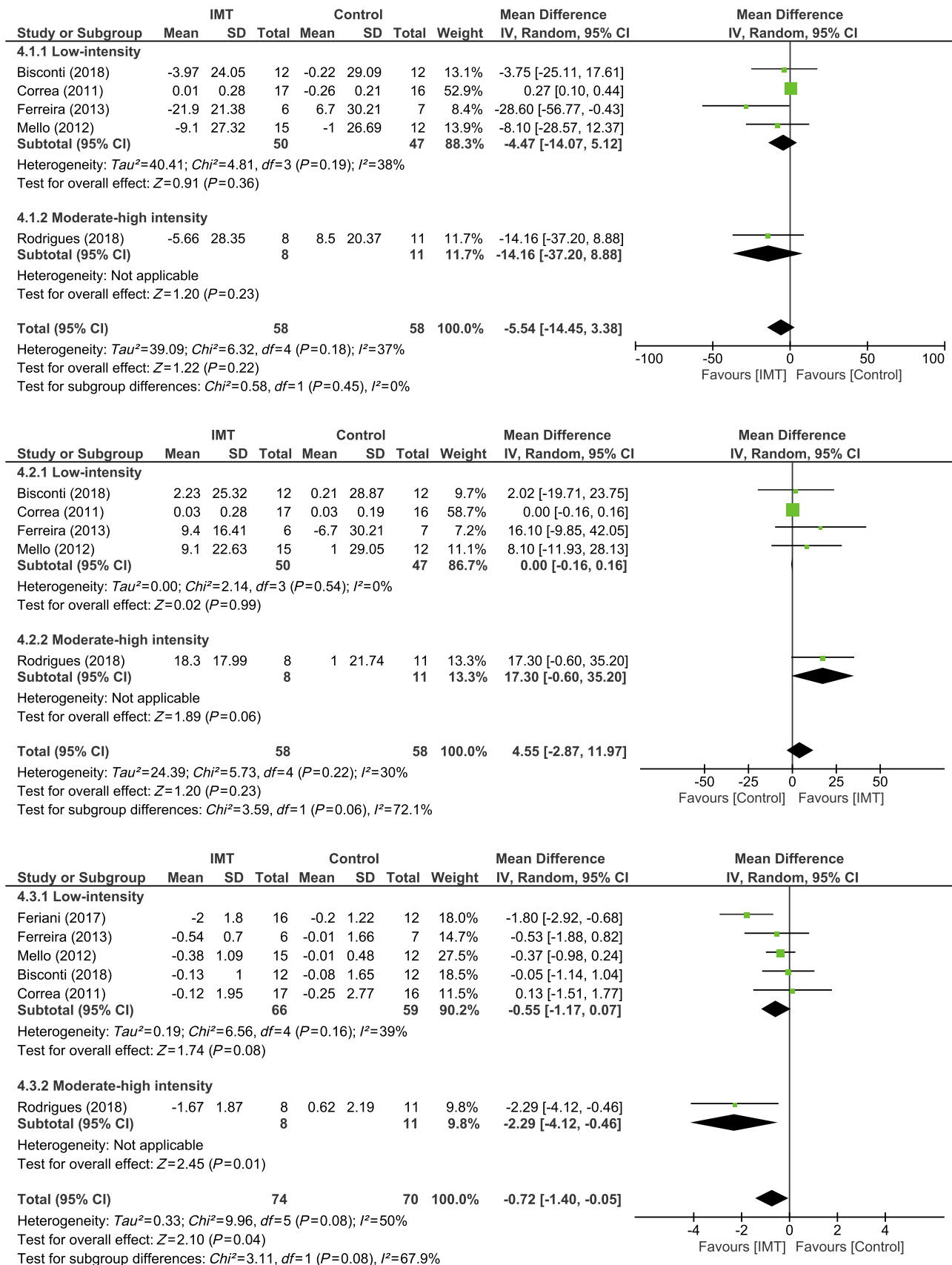


Figure 4 Forest plot depicts of inspiratory muscle training on (A) low-frequency heart rate variability, (B) high-frequency heart rate variability, and (C) low-to-high frequency ratio compared to low and moderate-high intensity.

Therefore, the results from its meta-analysis must be evaluated with caution. Most of the above mentioned pathophysiological conditions have been strongly associated with inspiratory muscle weakness (IMW). Patients with IMW are more susceptible to muscle fatigue and consequently to metabolite accumulation which activates unmyelinated type IV phrenic afferent fibers that increases sympathetic outflow reflex activity and produces a vasoconstrictor response in resting limbs which has been referred to as “inspiratory muscle metaboreflex overactivation.”⁴⁰

Cardiovascular effects of IMT have been associated with the respiratory maneuver performed during the training sessions which inflates the lungs near maximum respiratory capacity that may cause pulmonary parasympathetic stimulation, and consequently sympathetic activity reduction and an increase in blood flow to the limbs, resulting in a flush of metabolites and attenuation of vasoconstriction.⁴³ Therefore, in patients with essential hypertension, blood pressure reduction has been associated with sympathetic activation reduction and parasympathetic increase.⁹ Moreover, IMT has been associated with reduction in respiratory muscle oxygen demand/delivery mismatch and consequently reduces respiratory fatigue in heart failure patients.⁴⁰

Low versus moderate-high intensity IMT protocols appear to elicit differences in HR and DBP with low-intensity IMT protocols associated with a reduction in HR reduction, which might be related to the greater number of repeated respiratory maneuvers, not possible with moderate-high intensity IMT, that facilitated a reduction in sympathetic nervous system activity. Conversely, moderate-high intensity protocols are more likely to stimulate mechanoreceptors insofar as vascular occlusion as a result of muscle contraction which has been related to an increase in BP.⁴⁵

Clinical implications

The studies included in this meta-analysis found that IMT increases MIP and has a modest effect in only one of the HRV outcomes. IMT also decreased HR and DBP, but only in low or moderate-high intensity protocols alone. Cardiovascular patients were the main population in this review (6/10 studies).

Limitations

This present systematic review and meta-analysis have limitations that warrant consideration. The major

limitation is related to the limited number of publications eligible for consideration and poor to modest study quality. Another limitation regards the moderate to high degree of heterogeneity in the studies analyzed, which is likely related to the different patient populations and variable characteristics investigated in this small number of RCTs.

Conclusion

IMT is an effective treatment for inspiratory muscle weakness in several populations and according to this review might also be considered as a complementary treatment for cardiovascular modulation mainly for HR and DBP. Further studies are required to understand better the role of IMT as a component or alternative to regular exercise protocols.

Disclosure

The authors declare that there are no conflicts of interest in this work.

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