Effects of resistance added on aerobic training on autonomic function in cardiac patients

META ANALYSIS

ABSTRACT

Objective: Autonomic imbalance in patients with chronic heart failure (CHF) and cardiovascular diseases (CVD) is characterized by reduced parasympathetic and enhanced sympathetic activity. Aerobic exercise improves autonomic function in patients with CHF and CVD. However, little is known about the effects of resistance training (RT) on cardiac autonomic function. Therefore, we aimed to investigate the effects of RT added on aerobic training on autonomic function in patients with CHF and CVD.

Data sources: The relevant clinical trials were searched in PubMed, Physiotherapy evidence Database (PEDro, Science Direct and Google Scholar databases using the following keywords, "resistance or strength training", "chronic heart failure", "coronary artery disease", "myocardial infarction", "hypertension", "cardiovascular disease", "heart rate variability (HRV)", "heart rate recovery (HRR)", "muscle sympathetic nerve activity (MSNA)", and "autonomic function".

Data synthesis: Twelve articles with 323 subjects were eligible to be evaluated. The outcome measures included HRV, HRR, and MSNA. There were seven studies on CHF, two on CAD, and three studies on hypertension. Meta-analysis of all the studies showed that combined RT and aerobic training decreased MSNA significantly in patients with CHF and CAD (mean difference: -3.796; CI: -6.779 to 0.813; p=0.013; I^2=93.5%). No study evaluated the effects of RT or combined training on HRR.

Conclusion: We could not find sufficient data about the effects of RT alone on HRV and HRR, but the results showed that combined RT and aerobic training improved MSNA in patients with CHF and CAD, significantly. Further studies with similar methodological principles on the same patient population are needed.

Keywords: resistance training, autonomic function, chronic heart failure, heart rate variability

INTRODUCTION

Chronic heart failure (CHF) is the final stage of heart disease and one of the important reasons for morbidity and mortality globally (1, 2). The overall prevalence of HF is 1%-2% and increases with age, and therefore, is more than 10% in patients over 70-years (3).

CHF is a complex clinical syndrome with the left ventricle unable to fill with or eject blood owing to structural or functional impairment. Coronary artery diseases (CAD) and hypertension are two important causes of HF. The most important symptoms of CHF are fatigue, dyspnea, and exercise intolerance accompanied by a decreased quality of life (4). Autonomic imbalance, sympathetic activation, and vagal withdrawal, in CHF, results from biochemical alterations in central autonomic nuclei as well as the altered function of peripheral autonomic reflexes to improve cardiac output via increasing heart rate and stroke volume to compensate for perfusion problems. Prolongation of this condition becomes maladaptive and contributes to the progression of the disease and fatal events because of impairment of neuroendocrine and baroreceptor activation, which causes vasoconstriction increased oxygen consumption, and high hemodynamic load (5-7).

The autonomic function can be evaluated through baroreceptor sensitivity, measuring heart rate variability (HRV), heart rate recovery (HRR), and muscle sympathetic

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nerve activity (MSNA). HRV is defined as beat-to-beat variations in the heart rate of individuals with sinus rhythm, which has time and frequency domains. Time-domain parameters are the standard deviation of all RR intervals (SDNN), the standard deviation of average RR intervals (SDANN), root mean square of the difference in RR intervals (RMSSD), and percentage of NN intervals of more than 50 ms (pNN50) indicating parasympathetic activation. The frequency-domain includes high frequency (HF), low frequency (LF), very low frequency (VLF), and LF/HF ratio. HF represents the parasympathetic activity, whereas LF indicates the sympathetic activity and LF/HF represents autonomic balance (8). La Rovere et al. (9) showed that SDNN <70 ms could predict mortality in cardiac patients and a 10 ms increase in SDNN reduces mortality by 20%. HRR is another parameter that represents the vagal activity of autonomic function and can be measured 1- 6 minutes after exercise termination (10). Investigations have shown a decrease in HRV and an increase in MSNA in patients with CHF (11).

Although several studies confirmed the influence of aerobic exercise training alone (12-14) or in combination with resistance training (RT) (15, 16) on the improvement of the autonomic function in CHF, little is known about the effects of RT alone on autonomic function in patients with CHF and the limited data published have shown contradictory results (17, 18). Cider et al. (18) investigated the effects of five months of peripheral training program in CHF. Although a comprehensive type of resistance exercise including weight and pully training in the majority of muscle groups was used, no significant changes in HRV in CHF was reported in their study. However, there is evidence for the improvement of HRV following moderate-intensity resistance exercise and circuit resistance training in CHF (16, 17). Despite the fact that resistance activities are needed to carry out daily tasks in patients with cardiac disease, and in particular patients with CHF who suffer from severe muscle weakness and atrophy (19), there is no systematic review or meta-analysis evaluating the effects of RT alone or in combination with aerobic training on autonomic function in patients with CHF. As mentioned above, little evidence is available regarding the effects of RT on autonomic function in CHF. Therefore, studies that explored the effects of RT on autonomic function in conditions predisposing to HF including CAD and hypertension were also included. Given this knowledge gap, our objective in this systematic review was to `investigate the effects of RT or combined RT and aerobic exercise on autonomic function in patients with CHF and relevant conditions such as CAD and hypertension.

HIGHLIGHTS

- Combined resistance training (RT) and aerobic training improved muscle sympathetic nerve activity in patients with chronic heart failure and coronary artery disease (CAD).
- The positive impact of RT on autonomic function in CAD might be owing to less intensive approaches.
- The dose-response relationship of RT should be investigated in future studies.

METHODS

Search strategy
This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The relevant clinical trials were searched in PubMed, Physiotherapy evidence Database (PEDro, Science Direct, and Google Scholar databases using the following keywords, "resistance or strength training", "chronic heart failure", "coronary artery disease", "myocardial infarction", "hypertension", "cardiovascular disease", "heart rate variability (HRV)", "heart rate recovery (HRR)", "muscle sympathetic nerve activity (MSNA)", and "autonomic function". Eleven articles were eligible to be evaluated. The outcome measures included HRV, HRR, and MSNA. Two reviewers evaluated the articles independently according to the titles and abstracts to find eligible articles. The relevant studies were then evaluated precisely analyzing the full texts. The references of the retrieved articles and previous reviews were manually checked to identify additional eligible studies.

Selection criteria
Studies were included according to the following criteria, randomized controlled trials or quasi-experimental studies using RT or combined aerobic and RT training in adult patients of both sexes with CHF and related diseases such as CAD, myocardial infarction, and hypertension. Exclusion criteria were studies with one session training and patients with other concomitant diseases.

Data extraction
Data extraction was performed by two researchers (M.S. and R.R.). The following information was extracted from each study, first author, year of publication, number of participants enrolled men and women), patient characteristics, autonomic assessment principal, intervention details, and the results were extracted from the studies. When there were unclear data, missing data were obtained by contacting the authors, however, one author did not responde for detailed data to use in meta-analysis.

Evaluation of study quality
The methodological quality of selected trials was assessed by the PEDro scale. The PEDro scale scores 10 items, random allocation, concealed allocation, similarity at baseline, subject blinding, therapist blinding, assessor blinding, >85% follow-up for at least one key-outcome, intention-to-treat analysis, between-group statistical comparison for at least one key-outcome, and point and variability measures for at least one key-outcome. Items are scored as either present (1) or absent (0), and a score out of 10 is obtained by summation. Inter-rater reliability generalized kappa statistic of between 0.40 and 0.75 was reported for the PEDro scale (20).

Statistical analysis
Data were extracted from the studies, and the meta-analysis was constructed using STATA 13 and expressed as average difference using a random-effects model and 95% CI. An I-squared test was used for indication of variation in SMD attributable to heterogeneity.

RESULTS

Selection of studies

Among 1,436 articles that were identified through the database search and the reference lists of the preselected articles, 250 articles were selected after the removal of duplicated and irrelevant articles. Finally, 12 clinical trials, which met the inclusion criteria, were evaluated in this study. Figure 1 shows the PRISMA flow diagram of studies included in this review.

Study characteristics

The study design, patient population (303 patients), intervention details, and the outcomes of the included studies are shown in Table 1. The duration of interventions was between 4 -24 weeks.
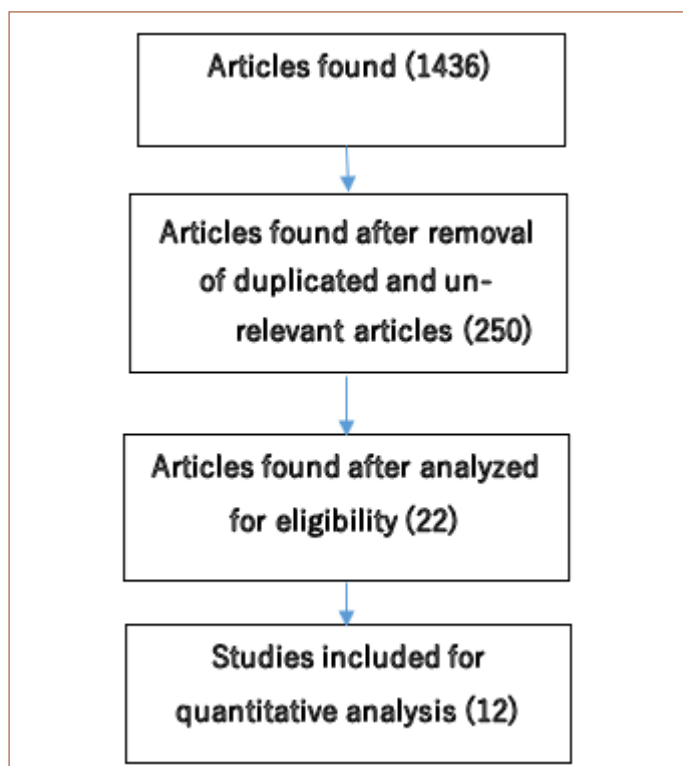

Figure 1. Flow diagram of included studies

There were seven studies (14-18, 21, 22) on CHF (194 patients, 128 men), two studies (23, 24) on coronary artery disease (64 patients, 43 men), and three studies (25-27) on hypertension (65 patients, 28 men). No study evaluated the effects of RT or combined resistance and aerobic training on HRR. In three studies on CHF, HRV, and three others, MSNA was assessed for evaluation of the cardiac autonomic system. One study on CAD assessed HRV, and another one assessed MSNA; and in all three studies on hypertension, HRV was assessed for evaluation of the cardiac autonomic system.

The intervention was RT in 5 studies (2 on CHF, 2 on hypertension, and 1 on CAD) and combined aerobic and RT in the rest of the studies. Training intensity was between 30%-80% of the one-repetition maximum (1RM) for RT. For combined training, the intensity of aerobic training was between 50%-80% of maximum HR or reserved HR or the HR considered up to 10% below the respiratory compensation point.

Quality assessment

The quality of selected trials assessed by the PEDro scale is presented in Table 2 and shows that the overall score of the evaluated studies is between 4 and 7. The mean score of the evaluated studies was 5.28 of 10, which indicates good quality of the studies.

As we did not have all the outcome measures in every article, we could not have a meta-analysis of all the studies together; therefore, meta-analysis was only for related articles.

Outcomes

The outcome measures included HRV assessed using ECG monitoring at rest, HRR assessed using exercise test, and MSNA assessed through neuromicrography.

The results of the meta-analysis are shown in Table 3. The results of the meta-analysis showed that MSNA decreased significantly (SMD=-3.796, 95% CI: -6.779 to -0.813; p=0.013) (Fig. 2); LF, HF, and LF/HF decreased whereas total power, SDNN, and RMSSD increased but not significantly (Table 3).

HRV: In one study on patients with CHF, only frequency-based parameters of HRV were evaluated before and after intervention without a control group (17). In one study on patients with hypertension, only frequency-based parameters of HRV were evaluated (26).
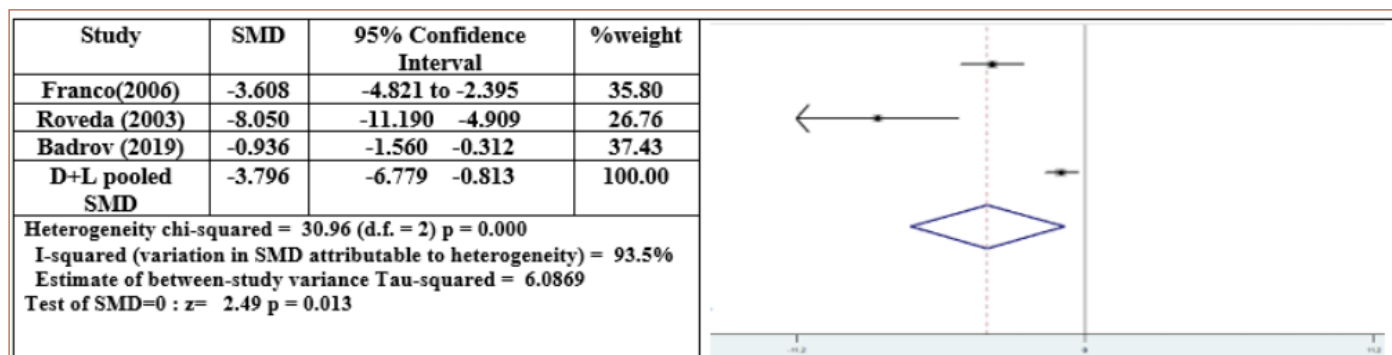
Study	SMD	95% Confidence Interval	%weight
Franco(2006)	-3.608	-4.821 to -2.395	35.80
Roveda (2003)	-8.050	-11.190 -4.909	26.76
Badrov (2019)	-0.936	-1.560 -0.312	37.43
D+L pooled SMD	-3.796	-6.779 -0.813	100.00

Heterogeneity chi-squared = 30.96 (d.f. = 2) p = 0.000
I-squared (variation in SMD attributable to heterogeneity) = 93.5%
Estimate of between-study variance Tau-squared = 6.0869
Test of SMD=0 : z= 2.49 p = 0.013

Figure 2. Muscle sympathetic nerve activity comparison between the CT group and combined aerobic and resistance training group

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Table 1. Summary of evaluated studies

Author (year)	Population characteristics	Groups: number, age	Autonomic assessment	Intervention	Results
Cider et al. (1997) (18)	CHF (NYHA II-III)	Exercise: 9 men, 12 women, age 61.8±9.8 years Control: 6 men, 12 women, age 64.7±5.3 years	24-hour Holter HRV: time/ frequency domain parameters	Exercise: Supervised hospital-based 60-minute circuit weight training at 60% 1-RM for 2 sets, 2 times a week for 20 weeks Control: usual care	No significant difference between the 2 groups in all HRV parameters
Roveda et al. (2003) (14)	Advanced heart failure	Combined n=7, 5 men; 64.6±4.8 Control n=9, 6 men 61.4±4.3	MSNA, microneurography	4 months, supervised exercise training program (three 60-minutes exercise sessions per week, at heart rates up to 10% below the respiratory compensation point. The bicycle work rate was increased by 0.25 or 0.5 kpm to return to the target HR levels, 25-40 min aerobic, 10 min of local strengthening exercises (sit-ups, push-ups, and pull-ups)	Dramatic reductions in directly recorded resting sympathetic nerve activity
Selig et al. (2004) (17)	CHF (LVEF <40%, NYHA class II—III)	Intervention: 19 (64±9) Control: 20 64 (65±13)	HRV(ECG), short-term (20 min supine)	Supervised hospital 3-months; 3/w multi-station hydraulic resistance training, leg cyclic ergometers and set of 5 stairs.	Significant changes in the HRV parameters. ↓LF and LF/HF, ↑HF. No changes in the control group. Mean R-R, SDNN and RMSSD were not different in either group
Jancik et al. (2004) (15)	CHF (LVEF <40%, NYHA class II—III)	10(65±13)	short-time, HRV(ECG)	Combined: Aerobic: 20 min anaerobic threshold, Resistance: 20 min 30%-60% 1RM, 8 weeks	↑total power of HRV
de Mello Franco et al. (2006) (21)	CHF (LVEF <40%, NYHA class II—III	Trained (n=17, 13 men) (56±2.9), untrained (n=12, 9 men) (52±2.2)	MSNA (peroneal nerve, microneurography)	MSNA (peroneal nerve, microneurography)	Significant reduction in MSNA in trained group after 4 -month training, but did not different after 4 months of home exercise.
Collier et al. (2009) (25)	Pre-hypertension	Aerobic: n=10, 49.2±1.6 Resistance: n=10, 46.7±1.8	HRV (frequencies domain) (ECG)	Aerobics: 3/week, 65% VO2 peak resistance: 3 times 10 repetitions for 4 weeks	Aerobics:↑ ln HF, ↓LF/HF Resistance:↓ ln HF,↑ LF/HF
Antunes-Correa et al. (2010) (22)	CHF (LVEF <40%, NYHA class II—III)	Men trained(n=12) (57±2), men untrained (n=10) (59±3), women trained (n=9) (57±2), women untrained (n=9) (60±3)	MSNA (peroneal nerve microneurography)	4 months Cycling (20-40 minutes, intensity of anaerobic threshold up to 10% below the respiratory compensation point obtained in the cardiopulmonary exercise test + 10 min RT)	Significant reduction in MSNA in trained group, no difference between sex, (exercise training effect, P=0.000002; sex effect, P=0.41)
Ricca-Mallada et al. (2012) (16)	CHF (LVEF <40%, NYHA class I-II	Training: 10 (59+7.92) control: 10 (56.5+8.43)	HRV (ECG), 12 min supine-polysomnography	6 months breathing exercises and free non-resistance arm (20 min), circuit RT using a mechanical bicycle (20 min, started with 50%-80% of the peak workload)	Training: ↑RR interval, HF, LF, the magnitudes of deceleration capacity and acceleration capacity control: no significant changes
Caruso et al. (2015) (23)	CAD (I, II)	RT: 10 (61+4.4) control: 10 (61.3+5.2)	HRV (ECG), 10 min supine HR recording by polar	Leg press 458 weeks, 3×20, 30% 1RM Leg press	↑strength, RMSSD, SD1, ApEn ↓HR

Table 1. Summary of evaluated studies (Continued)

Author (year)	Population characteristics	Groups: number, age	Autonomic assessment	Intervention	Results
Masroor et al. (2018) (26)	Sedentary hypertensive women	Combined aerobic and RT: n=15, 39.67±4.1 Control: n=13, 41.54±4.25	HRV (ECG)	4 weeks, combined aerobic (50%-80% HR max, 20 min) and resistance (50%-80% 1RM, 3×10, 5 exercise)	↓ In LF, LF/HF, SBP, DBP,↑HFnu, total power, SDNN, RMSSD in combined group
Trevizani et al. (2018) (27)	Treated hypertensive	n=9, 58.00±7.7	HRV (ECG), Polar	12 sessions, 8 exercises (leg extension, leg press, leg curl, bench press, seated row, triceps push-down, seated calf flexion, and seated arm curl) 2 sets of 15-20 repetitions, 50% 1RM, 2-minute rest intervals, 3 times a week	Reduced sympathetic-vagal balance (training interaction vs. group: *P*=0.058, ES=-0.83) in treated hypertensive subjects (↑ LF, LF/HF, ↓HF, RMSSD, SDNN)
Badrov et al. (2019) (24)	CAD	Combined aerobic and resistance: n=22, 62±8 control: n=22, 62±11	HRV (ECG), MSNA microneurography	6 months, 20 to 60 minutes, aerobic: % to 70% of HR reserve; resistance: 50% to 60%1RM, 1 to 3 sets at 10 to 15 rep, 8 to 12 exercise	No changes in HRV, significant reduction in MSNA after training, no differences in HRV existed between CAD post-cardiac rehabilitation and control

CAD - coronary artery disease, CHF - chronic heart failure, LVEF - left ventricular ejection fraction, ECG - electrocardiography, HF - high frequency band, HR - heart rate, HRV - heart rate variability, LF - low frequency band, LF/HF - low frequency to high frequency ratio, MSNA - muscle sympathetic nerve activity, RMSSD - Root mean square of successive RR interval differences, RT - resistance training, SDNN - Standard deviation of normal RR intervals

Table 2 . Risk of bias of evaluated studies based on PEDro- scale

Author (year)	Random allo-cation	Concealed allocation	Groups similarity at baseline	Patients' blindness	Care provider blindness	Assessor blindness	Drop out <15%	Intention to-treat analysis	Mean difference report	Measures of variability report	Total score
Cider et al. (1997) (18)	*					*	*	*	*		5
Roveda et al. (2003) (14)	*	*	*				*		*	*	6
Selig et al. (2004) (17)	*		*			*			*	*	5
Jancik et al. (2004) (15)			*				*		*	*	4
de Mello Franco et al. (2006) (21)	*	*	*				*		*	*	6
Collier et al. (2009) (25)	*	*	*				*			*	5
Antunes-Correa et al. (2010) (22)	*	*	*				*		*	*	6
Ricca-Mallada et al. (2012) (16)	*	*	*			*	*				5
Caruso et al. (2015) (23)	*	*	*		*	*			*	*	7
Masroor et al. (2018) (26)	*	*	*			*	*		*	*	7
Trevizani et al. (2018) (27)	*	*	*				*		*	*	6
Badrov et al. (2019) (24)			*				*		*	*	4

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Table 3. Meta-analysis of the studies, random effect model

Outcome measure	Studies analyzed	Number in intervention	Number in control	I Effect (95% CI)	P-value	i^2 (%)	SMD
LF, ms^2	6	86	85	-0.504, 0.478	0.96	59.4	-0.013
HF, ms^2	6	86	85	-0.650, 0.739	0.90	78.8	-0.044
LF/HF	5	64	63	-0.907, 0.419	0.471	69.4	-0.244
MSNA ms^2	3	46	43	-6.779, -0.813	**0.013**	93.5	-3.796
Total power, ms^2	3	35	33	-2.932, 7.960	0.380	96.3	2.379
SDNN, ms	4	66	65	-0.195, 1.466	0.134	80.1	0.635
RMSSD, ms	4	66	65	-0.055, 1.325	0.071	71.3	0.635

HF - high frequency band, LF - low frequency band, LF/HF - low frequency to high frequency ratio, MSNA - muscle sympathetic nerve activity, RMSSD - Root mean square of successive RR interval differences, SDNN - Standard deviation of normal RR intervals

MSNA: In four studies, MSNA was assessed using peroneal nerve microneurography with combined RT and aerobic training intervention. Three studies were conducted in patients with CHF with the same protocol included 4 months of combined exercise training (20-40 minutes of aerobic training and 10 minutes of RT) (14, 21, 22). The other one was conducted on patients with CAD with the same intervention but for 6 months and showed a significant reduction of MSNA after the intervention (24). Besides, the data of one study in patients with CHF could not be included in the meta-analysis because it was presented in a graph and its author didn't answer to our request for detailed data (23).

In studies about CHF, four studies indicated the effects of RT on HRV; one of them had no effect on HRV (18), the second one showed improvement of the frequency-domain parameters (17), another one showed improvement of total power (15), and the last one indicated increasing R-R interval, LF, and HF (16). Three studies indicated a decrease in MSNA after combined resistance and aerobic training.

In studies about CAD, one study indicated the improvement of HRV after RT (23), and another one showed a decrease in MSNA after combined training (24).

In studies about hypertension, one study showed improvement of HRV after combined training whereas two showed a reduced sympathetic-vagal balance after RT.

DISCUSSION

This study is the first meta-analysis, which provides information about the effects of RT alone or in combination with aerobic training in patients with CHF and relevant conditions including CAD and hypertension. The results showed that RT alone or in combination with aerobic training improved sympathovagal balance.

Autonomic balance assessment through measuring different variables indicating sympathetic or parasympathetic activation has an important predictive role in patients with CHF (8). It also has an important role in managing exercise programs and determining exercise intensity for these patients (12). Reducing HRV indicates autonomic imbalance and predicts mortality in patients with CHF regardless of CHF type; thus, the improvement of HRV should be considered in patients with CHF (28-31). Several studies have shown that exercise training is an effective non-pharmacological strategy to improve autonomic function in patients with CHF, CAD, and hypertension besides medical treatments such as beta-blockers (32-34). According to the studies that have evaluated autonomic function by measuring HRV and norepinephrine, aerobic exercise reduces sympathetic activity and increases vagal activity. Consequently, it could reduce systemic vascular resistance, improve perfusion, and increase the vascular density of muscles (14, 35). It seems these effects are owing to the improvement of endothelial function regulation of nitrite-oxide synthesis, and reduced angiotensin II (36-38).

A systematic review by Hsu et al. (39) has shown HRV and HRR are non-invasive criteria for autonomic function in response to exercise in class II and III of patients with CHF. The results of that study indicated that exercise improved HRV and HRR.

Chronic heart failure

Thus far, only two studies assessed the effects of RT on HRV in patients with CHF in which, one study did not affect HRV and the other only the frequency-domain improvement were observed. Selig et al. indicated that three months of moderate-intensity RT by using a hydraulic resistance training machine improved only the HF parameter of HRV, with no significant effect on time-domain parameters (17). A study by Cider et al. (18) showed that 20 weeks of RT with 60% 1RM (2 sessions/week), did not significantly change HRR and HRV, in patients with CHF.

Jancik et al. (15) showed that after 8 weeks of combined exercise training in patients with HF (functional class II and III), the total power of HRV, maximum load, metabolic equivalent, and peak VO2 improved, significantly. In addition, other frequency domain parameters of HRV improved, but the changes were not statistically significant. Each exercise session included 20 minutes of aerobic training with the intensity of anaerobic threshold and 20 minutes RT with intensity at 60% 1RM (in the first 2 weeks, the intensity was 30% 1RM). They concluded that HRV assessment could be a helpful tool for evaluating the effectiveness of exercise training in cardiac rehabilitation programs.

Ricca-Mallada et al. (16) have shown increasing in LF, HF, and R-R interval and SDNN after 24 weeks of exercise training in patients with CHF with functional class I and II. Each exercise session included 20 minutes of breathing exercises and

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free nonresistance exercise and 20 minutes of circuit resistance training using a mechanical bicycle with intensity at 50%-80% of the peak workload from the exercise test for 24 weeks (16).

Three studies showed an improvement in MSNA after combined resistance and aerobic training. Roveda et al. (14) showed that exercise training in 16 patients with HF (class II and III) resulted in dramatic reductions of directly recorded resting sympathetic nerve activity. MSNA was not greater than in trained, healthy controls (14). In another study by de Mello Franco et al. (21), 4 months of supervised combined exercise training (20-45 minutes aerobic exercise and 10 minutes RT) improved peak VO2 and decreased MSNA significantly in patients with CHF (21). However, the changes of the outcome measures after the next 4 months of unsupervised exercise training were not different from the baseline, and the effects of the first 4 months' exercise training were not sustained. Consequently, it seems that supervision is important to maintain the exercise intensity to have significant improvement in peak VO2 and MSNA. Although the adherence of the patients was acceptable, the peak VO2 decreased after the second 4 months period of unsupervised exercise training (14).

Antunes-Correa et al. (22) evaluated the effects of 4 months of combined exercise training, in 4 groups of patients with CHF (trained and untrained women and men). The exercise program included 20 -40 minutes of aerobic exercise and 10 minutes RT in each session, 3 sessions per week for 4 months. The results showed significant improvement of peak VO2 and decrease in MSNA in trained compared with those in an untrained group; however, there was no difference between men and women. Moreover, there was a strong relationship between reduced MSNA and increased peak VO2 (22).

According to the above-mentioned studies, it seems that, combined aerobic and RT could decrease MSNA in patients with CHF; however, considering the high heterogeneity (I^2=93.5%) of these studies, it may be inappropriate to derive an estimate of the overall effect from that particular set of studies. More heterogeneous studies are needed for a concise conclusion. We cannot also conclude that RT alone had the same positive effects as combined exercise training in patients with CHF.

Furthermore, there is controversy about the effects of RT alone on HRV (17, 18). The RT duration in each session was 10 minutes which seems to be short and the details of the RT program was not described (14, 21, 22).

Coronary artery disease
One study indicated improvement in HRV after RT in patients with CAD (23) and another showed reduction in MSNA after combined training in these patients (24).

A study by Caruso et al. (23), demonstrated the effects of 8 weeks of RT (low load, high repetition, 3 sets of 20 repetitions, 30% 1RM) using leg press in men with CAD. Of course, all the patients participated in aerobic exercise training for 1 year before the RT program and continued this program during the RT intervention. The results showed improvement of RMSSD, SD1, ApEn, and muscle strength and reduction of heart rate.

Badrov et al. (24) has recently investigated the effects of 6 months of combined aerobic (20 to 60 minutes of exercise at 40% -70% of HR reserve) and RT in 22 patients with CAD during a cardiac rehabilitation program. RT consisted of 8 to 12 exercises, 1 to 3 sets at 10-15 repetitions with the intensity of 30%-60% 1RM for upper and lower body muscles that increased gradually (~5%) once the upper limit of 12-15 repetitions could be completed, comfortably. Marked improvement in baseline autonomic function and neuro-cardiovascular stress reactivity in these patients were reported. Blood pressure and MSNA decreased, however, cardiovagal BRS and HRV did not change significantly, perhaps owing to modest improvement in fitness. These results are in contrast with other studies, perhaps owing to the similar severity of impairment of HRV indices in this study population to the healthy control group.

In the above-mentioned studies, the exercise training intensities were not so high. Therefore, the positive impact of RT on autonomic function in patients with CAD might be because of the less intensive approaches.

Hypertension
Three studies indicated improvement of HRV after RT and combined training in patients with hypertension. Collier et al. (25), evaluated the effects of 4 weeks of aerobic (30 minutes of treadmill exercise, 3 days per week at 65% of their VO2peak) versus RT (isolating 9 major muscle groups, 3sets of 10 repetitions) in patients with mild hypertension. The results of their study demonstrated that aerobic exercise improved the autonomic nervous system by increasing vagal tone, reducing sympathovagal balance, and increasing baroreceptor sensitivity (BRS) whereas RT did not improve cardiac autonomic tone and decreased BRS. LF, HF, or total power did not change significantly with either exercise training type. The LF:HF ratio decreased significantly with aerobic exercise and increased with RT but was not significant. The results suggest that aerobic exercise training decreases sympathetic modulation and increases vagal modulation, whereas RT training decreases sympathetic modulation to peripheral blood vessels, also decreasing parasympathetic modulation of the heart through finger plethysmography.

In another study, 4 weeks of combined aerobic exercise training (20 minutes with the intensity of 80% maximum heart rate) and RT (50%-80% 1RM, 3 sets, 10 repetitions of 5 exercises) improved HF, SDNN, total power, and RMSSD and decreased LF, LF/HF, and systolic and diastolic BP in pre-hypertensive women (26).

A recent study showed a statistically significant reduction in post-exercise systolic BP in both treated hypertensive and normotensive groups (p=0.040), without significant change in resting BP along with RT program (p=0.159) and a reduced sympathetic-vagal balance (training interaction vs. group: p=0.058, effect size=−0.83) and after 4 weeks RT with the intensity of 50% 1RM in patients with treated hypertension. This low intensity of RT was safe and promoted slight im-

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provement in cardiac autonomic balance only in the hypertensive group (27). It appears that the small sample size and short duration of the intervention as well as the low intensity of RT probably contribute to insignificant changes in HRV indices. A longer duration of the RT program may result in significant improvement of HRV parameters.

Del Pozo-Cruz et al. (40) demonstrated that there was a threshold dose for exercise intensity, and higher intensity was not accompanied by more improvement in quality of life necessarily. In that study, the intensity of aerobic exercise was divided into 4 quartiles on the basis of energy consumption per week, and the best score for quality of life was obtained at the second quartile, which was 349-510 kcal per week. Illamo et al. (41) have shown that HRV response is dose-dependent; therefore, the best results are obtained with moderate-intensity aerobic exercise, and the graph of SDNN-intensity of exercise is bell-shaped. The dose-response relationship of RT on HRV indices should be evaluated in future studies (15). Gonçalves et al. in 2015 (42) evaluated the effects of 1 session of RT with 2 different intensities (40% and 80% 1RM) on HRV in active healthy men. The protocol of the study included 2 sets of 20 repetitions for the intensity of 40% 1RM and 2 sets of 8 repetitions for the intensity of 80% 1RM. He indicated that during the first 20 minutes, HRV parameters did not change compared with the rest; however, after 20 minutes, HRV increased, and there was no difference between the 2 intensities. However, their study evaluated the acute effects of 2 different models of RT on HRV.

A meta-analysis by Pearson et al. in 2017 (43) showed that exercise training improved RMSSD and HF, both of which represent the parasympathetic activity of the autonomic system in patients with HF. They included 20 studies in their meta-analysis with different types of exercises such as RT (15, 16) aerobic training, combined resistance, and aerobic training, yoga (44), and respiratory exercise training (35); but only two of them evaluated the effects of RT on HRV in patients with CHF. The exercise intensity in most aerobic programs was moderate (40%-70% maximum heart rate or reserved heart rate (33, 41, 42) and only in one of them, the exercise intensity was 60%-80% reserved heart rate (45), and intensity in RT programs was reported as moderate (60%1RM). Ricca-Mallada et al. (13) demonstrated that HRV could be a valuable, helpful, predictive, and cost- effective indicator for screening patients with CHF (class I, II, and III) who could benefit more from cardiac rehabilitation programs. According to his study, patients with baseline RMSSD <20 ms and HF <150 ms^2 Hz could have more improvement in ejection fraction, 6-minute walking test, and HRV parameters after aerobic training with the intensity of 50%-80% maximum heart rate (13). Another study indicated that RT and aerobic training had the same influence on HRV in patients with type 2 diabetes. The intensity of exercise was 60%-65% heart rate reserved in the aerobic training group and 70%-80% 1RM in the RT group (46).

Study limitations
This is the first study evaluating the effects of RT alone or in combination with aerobic training on autonomic function in

patients with CHF and relevant conditions, including CVD and hypertension. However, this study had some limitations such as different populations; different outcome measures for evaluating the autonomic system; different exercise training programs in terms of the type, intensity, and duration, which implies that more investigations and clinical trials are needed in each area for arriving at a more reasonable conclusion.

CONCLUSION

The results of this study showed that combined RT and aerobic training significantly improved MSNA in patients with CHF and CAD. However, further studies with a homogeneous patient population are needed.

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