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The effect of functional electrical stimulation of the legs on cardiopulmonary function and quality of life in patients with chronic heart failure: A systematic review and meta-analysis

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Abstract

Introduction: Functional electrical stimulation is important for the rehabilitation of patients with chronic heart failure. This meta-analysis of randomized controlled trials compared the efficacy of functional electrical stimulation versus conventional exercise training or placebo in patients with chronic heart failure.

Methods: Studies were searched through PubMed, Embase, and the Cochrane Library databases up to 1 November 2023. The outcomes were cardiopulmonary function index (6-minute walking distance), peak oxygen consumption, and Minnesota Heart Failure Life Questionnaire quality of life scores. A subgroup analysis was conducted according to the ejection fraction. The 95% confidence interval and mean difference represented the outcome of the effect size.

Results: Seventeen studies involving 732 participants were included. Compared with the control, functional electrical stimulation significantly improved peak oxygen consumption (MD = 2.84 ml/kg/min, 95% CI: 1.99–3.68 ml/kg/min), increased 6-minute walking distance (MD = 49.52 m, 95% CI: 22.61–76.43 m), and improved the life quality scores (MD = −12.86, 95% CI: −17.48 to −7.88). Compared with functional electrical stimulation, exercise training also improved peak oxygen consumption (MD = −0.94 ml/kg/min^{-1}, 95% CI: −1.36 to −0.52 ml/kg/min), and the quality of life (QoL, MD = 0.66, 95% CI: 0.34–0.98, $p < 0.05$, $I^2 = 38\%$), but the result of 6-minute walking distance (MD = −6.97 m, 95% CI: −18.32 to −4.38 m) did not show a difference. Further subgroup analysis showed that outcomes including the above, significantly improved under the functional electrical stimulationfor both HF patients with reduced ejection fraction and HF patients with preserved ejection fraction patients, but difference is insignificant of the results between groups of aerobic exercise and functional electrical stimulationacted on patients with HF patients with reduced ejection fraction.

Conclusions: Our study demonstrates that compared with placebo, functional electrical stimulation benefits the patients with chronic heart failure on cardiopulmonary function and quality of life. Furthermore, HF patients with reduced ejection fraction patients benefit more from functional electrical stimulation than HF patients with reduced ejection fraction patients. Therefore, functional electrical stimulation is a promising complementary therapy for patients with chronic heart failure.

Keywords

Functional electrical stimulation, exercise training, heart failure, cardiopulmonary function, cardiac rehabilitation

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Introduction

Chronic heart failure (CHF), impacting over 20 million individuals, has significantly contributed to the escalating global health crisis. Given the increasing population of individuals aged 65 and older, the prevalence of CHF and the associated treatment costs are estimated to rise exponentially over the next decade.[1] CHF is the most universal advanced-stage cardiovascular disease with high mortality

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and a high re-hospitalization rate. Patients with CHF are usually accompanied by declined aerobic exercise capacity, poor quality of life (QoL), and frequent re-hospitalization, which cause a huge economic burden to the patients and the society.[2] Exercise rehabilitation training is an effective and relatively low-cost approach to solve these problems. However, patients with CHF often struggle to adapt and consequently discontinue aerobic exercise training programs.

Exercise therapy may not be an appropriate therapy for the patients with advanced CHF due to their extreme exercise intolerance. Recent studies have reported that functional electrical stimulation (FES), characterized by high compliance and suitability for home use, could improve the prognosis of CHF by stimulating muscle contraction. Some other additional evidences have also shown its promise in reducing the health burden associated with CHF.[3–6] Therefore, FES may serve as an alternative treatment for patients who struggle to adapt to aerobic exercise. In fact, a previous meta-analysis has shown the effectiveness of passive (e.g., FES) or active exercise on patients with CHF.[7] This study aimed to update data regarding the effectiveness of aerobic exercise and FES on the patients. Furthermore, this study designated to explore the differences in outcomes among patients with varying ejection fractions who underwent the aforementioned rehabilitation treatments. Therefore, we carried out a systematic review and meta-analysis to investigate whether FES has positive clinical impacts on the cardiopulmonary function and QoL of patients with CHF.

Methods

Articles were searched from databases PubMed, Embase, and the Cochrane Library without language restrictions. This study has been registered on PROSPERO (registration no. CRD42023478437).

A mix of medical subject headings (MeSH) and keywords were used to search relative articles. The following keywords were used in the searching process: "heart failure," "chronic heart failure," "HF" or "CHF" for patients type; "electrical stimulation," "FES" or "electrical muscle stimulation" for intervention category. Finally, the databases were artificially searched again. Specific search strategy is shown in Additional File 1. The search encompassed all the above-mentioned databases from 1 November 1993 to 1 November 2023. This systematic review was carried out in accordance with the Cochrane Collaboration Handbook[8] and PRISMA-2020.[9] The Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) is shown in Additional File 2.

Inclusion criteria

To select articles that adhere to the inclusion criteria, the full texts of all retrieved essays were individually scanned by two researchers to confirm relevance. (1) The patients were diagnosed with CHF by physicians; (2) The class of New York Heart Association (NYHA) was not less than class II; (3) Trials in all the articles were randomized controlled trials (RCTs); (4) Interventions were FES versus placebo or aerobic exercise versus FES; (5) Muscles in the legs were the sites where FES was applied.

Exclusion criteria

(1) Duplicate data were removed by inclusion of the most recently published article; (2) Articles not published in peer-review journals (e.g., conference papers, doctor theses, reports) were excluded; (3) the articles explained that FES and aerobic exercise coexist in one intervention group were excluded.

Study selection and data extraction

Duplicated articles were excluded at first. Irrelevant articles were ruled out by a reviewer (ZR) through reviewing the titles and abstracts, followed by articles selection according to their contents. The eligible articles were subsequently evaluated and selected by two reviewers (CJ and WYM) independently. Disagreement was resolved by discussing with the fourth reviewer (LQ). Data were extracted covering the authors, published year, population of patients, follow-up results, intervention methods, different types of study outcomes, and confounding factors for each study summarized in Tables 1 and 2, and Supplemental Table 1. Control was divided into the placebo group composed of routine daily life and sham FES and the exercise group composed of aerobic training and routine rehabilitation treatment. The intervention group was composed of FES only. All the patients received necessary medicine treatment for CHF. The final outcomes included peak oxygen consumption (peak VO_2), 6-minute walking distance (6WMD), and Minnesota Heart Failure Life Questionnaire.

Quality of research assessment

The assessment was carried out by two reviewers independently, and disagreement was resolved by discussing with another reviewer. The Cochrane risk-of-bias assessment tool was used for randomized trials.[27] The results were assessed with three potential judgments—"low risk of bias," "high risk of bias," or "some concerns." The risk of bias for included studies was assessed according to the appendix by RevMan (version 5.3, The Cochrane Collaboration, London, UK).

Data synthesis and analysis

The primary outcome measures in this study were consisted of two parts. The first part as the cardiopulmonary function results included peak VO_2 and 6WMD. These are objective

Table 1. Summary of baseline patients characteristics of included studies.

Study	Groups	Age (years)	Male (%)	BMI	NYHA (II/III/IV)	LVEF (%)
Deley et al.[10]	FES ($n=22$)	55 ± 10	73	25.9 ± 3.8	9/12/1	23.7 ± 7.4
	Cycle ($n=22$)	56 ± 7	86	27 ± 7.1	11/11/0	23.2 ± 10.6
Deley et al.[11]	FES ($n=12$)	56 ± 8	75	25.7 ± 3.7	9/3/0	28.2 ± 9.2
	Cycle ($n=12$)	57 ± 6	92	25.5 ± 9.6	9/3/0	26.3 ± 9.5
Dobsák et al.[12]	FES ($n=15$)	56 ± 67	71	28.3 ± 3.9	22/8/0	34.7 ± 5
	Cycle ($n=15$)	18.1 ± 3.9				
Eicher et al.[13]	FES ($n=12$)	54 ± 9	79	N/A	4/20/0	N/A
	Cycle ($n=12$)					N/A
Harris[14]	FES ($n=22$)	63 ± 10	77	N/A	17/5/0	28.3 ± 6.3
	Cycle ($n=24$)	62 ± 11	88		18/6/0	32.0 ± 9.3
Soska et al.[15]	FES ($n=29$)	57.3 ± 1.6	52	28.3 ± 0.9	18/5/0	30.1 ± 1.3
	Cycle ($n=26$)	63.5 ± 1.4	92	29.2 ± 0.7	19/4/0	34.9 ± 1.4
Palau et al.[16]	FES ($n=15$)	75 ± 10	40	31.5 ± 4.4	N/A	68 ± 11
	Cycle ($n=15$)	72 ± 9	47	30.5 ± 4.3		70 ± 9
	Control ($n=13$)	75 ± 9	31	34.8 ± 5.4		66 ± 8
Karavidas et al.[17]	FES ($n=16$)	57 ± 15	85	26.6 ± 4.8	12/4/0	27.5 ± 6.5
	Control ($n=8$)	64 ± 8	88	28.1 ± 3.7	6/2/0	27.2 ± 4.5
Karavidas et al.[18]	FES ($n=20$)	62 ± 12	80	27 ± 5	15/5/0	28 ± 7
	Control ($n=10$)	64 ± 8	80	28 ± 4	8/2/0	27 ± 5
Nuhr[19]	FES ($n=15$)	53 ± 7	97	26.2 ± 3.7	5/8/2	22 ± 3
	Control ($n=17$)	53 ± 13	82	27.5 ± 5.1	2/13/2	21 ± 7
Quittan et al.[20]	FES ($n=17$)	59 ± 6	71	22.7 ± 3.2	4/10/3	15.1 ± 3.1
	Control ($n=16$)	57 ± 8	56	25.7 ± 3.9	4/9/3	18 ± 5.2
Vaquero et al.[21]	FES ($n=7$)	59 ± 5	85	26.3	Post-transplant	N/A
	Control ($n=7$)	54 ± 8	71	26.2	Post-transplant	N/A
Parissis et al.[22]	FES ($n=15$)	75.2 ± 3.68	73	N/A	5/10/0	27.3 ± 3.2
	Control ($n=15$)	75.2 ± 3.32	60		6/9/0	28 ± 2.5
Karavidas[23]	FES ($n=15$)	69.4 ± 8.6	40	28.2 ± 4.42	11/4/0	N/A
	Control ($n=15$)	68.5 ± 7.9	40	28.3 ± 4.38	10/5/0	
Kadoglou et al.[4]	FES ($n=60$)	72 ± 7	55	27.2 ± 3.92	41/19/0	27.7 ± 4.5
	Control ($n=60$)	70 ± 11	58	24.4 ± 3.53	35/25/0	28.9 ± 4.7
Groehs et al.[24]	FES ($n=15$)	54 ± 2	93	22 ± 1	0/0/15	22 ± 1
	Control ($n=15$)	49 ± 2	87	25 ± 1	0/0/15	22 ± 1
Ennis et al.[25]	FES ($n=30$)	66.5 ± 7.8	67	30.1 ± 4.9	24/6/0	39 ± 11
	Control ($n=30$)	66.8 ± 13.5	73	27.8 ± 4.8	22/8/0	22 ± 12
Poltavskaya et al.[26]	FES ($n=22$)	64.5 ± 11.0	68.2	N/A	0/17/5	32.3 ± 3.5
	Control ($n=23$)	68.9 ± 9.0	47.8	N/A	0/19/4	30.8 ± 6.1

FES: functional electrical stimulation; N/A: not applicable.

indicators to assess the cardiac function of the patients with CHF and important predictors for prognosis of CHF. The second part was the QoL. The effect size measuring therapeutic impacts was assessed by the mean difference change between pre- and post-FES therapy. Because of the multiple research methods used in the selected RCTs, a random effects model was used for analyzing the pooled data according to the Cochrane Collaboration Handbook. $I^2 < 40\%$ was considered not affecting the results; $30\% < I^2 < 60\%$ indicated moderate heterogeneity of the results; $60\% < I^2 < 80\%$ indicated substantial heterogeneity of the results; $80\% < I^2$ indicated huge heterogeneity of the results. Subgroup analysis was conducted to analyze the therapeutic effect of FES compared with placebo or aerobic exercise according to different ejection fractions of the patients with CHF. This meta-analysis was conducted by RevMan (version 5.3) and Stata 16.0.

Results

The selection process of this study is shown in Figure 1. A total of 18 RCTs[4,10–26] comparing the effects of FES and control treatment on patients with CHF met the eligibility criteria for both qualitative and quantitative analyses. The quality of the included studies is shown in Supplemental Figure 7. Sixteen of the included articles reported HF patients with reduced ejection fraction (HFrEF), while two articles reported HF patients with preserved ejection fraction (HFpEF). Six studies were based on comparing FES

Table 2. Adverse events, study withdrawals, and reported symptoms.

Study	Groups	Location	Included/ recruited	Completed exclusions/adverse events
Deley et al.[10]	FES ($n=22$)	Home	46/44	No significant injury or muscle pain reported
	Aerobic ($n=22$)	Lab		2 excluded—lack of compliance during first 2 weeks of exercise training
Deley et al.[1]	FES ($n=12$)	Home	24/24	No significant injury or muscle pain reported
	Aerobic ($n=12$)	Lab		
Dobsák e al.[12]	FES ($n=15$)	Home	30/30	No significant pain or health complications (skin burns or muscle damage) reported
	Aerobic ($n=15$)	Lab		No adverse events reported
Eicher et al.[13]	FES ($n=12$)	Home	24/24	No significant harmful effects (sudden BP or HR changes, skin burns or muscle damage) reported
	Aerobic ($n=12$)	Lab		No adverse events reported
Harris[14]	FES ($n=22$)	Home	49/46	1 death—following randomization (severe heart failure), 1 withdrew—worsening symptoms of heart failure
	Aerobic ($n=24$)	Home		1 withdrew—assigned to the bicycle group dropped out of the study due to back discomfort
Soska et al.[15]	FES ($n=29$)	Home	86/71	No significant injury or muscle pain reported
	Aerobic ($n=26$)	Clinic		7 withdraw-loss of motivation, 6 exclude-admitted irregular EMS application for a period longer than 1 week, 2 withdraw-due to a change of residence
Palau et al.[16]	FES ($n=15$)	Physio dept. at hospital	59/52	2 withdrew-patients died; 5 withdrew-due to other reasons
	Aerobic ($n=15$)			
	Control ($n=13$)			
Karavidas et al.[17]	Control ($n=13$)	Physio dept. at hospital	24/24	No adverse events reported
	FES ($n=16$)			
Karavidas et al.[18]	Control ($n=8$)	Physio dept. at hospital	30/30	No adverse events reported
	FES (n=20)			2 withdrew—urgent heart transplantation
Nuhr[19]	Control ($n=10$)	Home	34/32	No adverse events reported
	FES ($n=15$)			
Quittan et al.[20]	Control ($n=17$)	Home	42/33	1 death—due to renal failure, 2 withdrew—urgent heart transplantation, 1 withdrew—received left ventricular assist device
	FES ($n=17$)			1 death—sudden death, 1 withdrew—urgent heart transplantation, 3 withdrew—non-urgent heart transplantation
Vaquero et al.[21]	Control ($n=16$)	Physio dept. at hospital	14/14	No adverse events reported
	FES ($n=7$)			
Parissis et al.[22]	Control ($n=7$)	Home/hospital	30/30	No adverse events reported
	FES ($n=15$)			
Karavidas[23]	Control ($n=15$)	Physio dept. at hospital	30/30	No adverse events reported
	FES ($n=15$)			
Kadoglou et al.[4]	Control ($n=15$)	Home	120/116	No adverse events reported
	FES ($n=60$)			4 withdraw-due to personal reasons
Groehs et al.[24]	Control ($n=60$)	Hospital	30/30	No adverse events reported
	FES ($n=15$)			
Ennis et al.[25]	Control ($n=15$)	Home/hospital	60/48	No adverse events reported
	FES ($n=30$)			
Poltavskaya et al.[26]	FES ($n=22$)	Hospital	45/37	1-HF hospitalizations, 1-refuse to attend
	Control ($n=23$)			3-HF hospitalizations, 3-refuse to attend

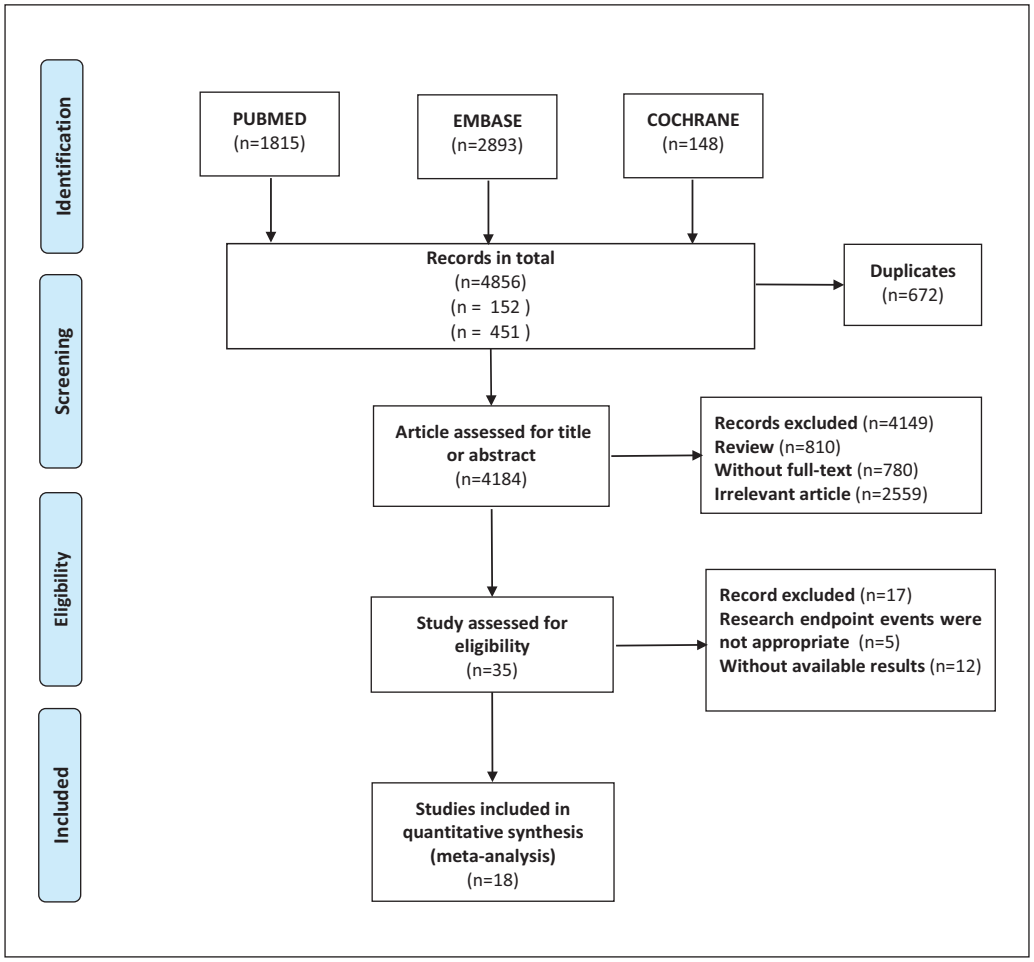

Figure 1. PRISMA flow diagram.

with cycle (including aerobic exercise, cycling training, etc.), and 10 studies were based on comparing FES with control (including normal care and sham FES). Characteristics of the patients are listed in Tables 1 and 2, and Supplemental Table 1.

Compared with the control group, FES elicited significant improvements on peak VO_2 (MD = 2.84 ml/kg/min, 95% Cl: 1.99–3.68 ml/kg/min; Figure 2), 6MWD (MD = 49.52 m, 95% Cl: 22.61–76.43 m; Figure 3), and standardized MHFLQ scores (MD = −12.86, 95% Cl: −17.48 to −7.88; Figure 4). However, FES could not improve peak VO_2 as much as aerobic training did (MD = −0.94 ml/kg/min, 95% Cl: −1.36 to −0.52 ml/kg/min; Figure 5). FES treatment and exercise therapy shared the nearly same effect on 6MWD (MD = −6.97 m, 95% Cl: −18.32 to 4.38 m; Figure 6). Meanwhile, compared with aerobic training, FES had no advantage on improving the QoL (MD = 0.66, 95% Cl: 0.34–0.98, $p < 0.05$, $I^2 = 38\%$; Figure 7).

We found that FES significantly improved the clinical outcomes (i.e., peak VO_2, 6MWD, and MHFLQ) in all types of HF patients, in comparison with the control group (Figures 2–4). Minor differences in the improvement of peak VO_2, and MHFLQ were found between FES and aerobic training, while no significant difference in the improvement of 6WMD was found.

Based on the subgroup analysis, FES significantly improved the aforementioned outcomes in both the patients with HFrEF and those with HFpEF. However, the patients with HFrEF who underwent exercise training had better peak VO_2 and QoL improvements than those who underwent FES. FES and exercise training shared same effects on improving peak VO_2 and QoL in the patients with HFpEF (Figures 5 and 7). Partial results displayed their relatively high heterogeneity. To ensure the robustness of the results, we conducted additional sensitivity analyses (Supplemental Figures 1–6), which reaffirmed their statistical reliability. The detailed results of the risk of bias assessment are listed in Supplemental Figure 7.

Discussion

Our meta-analysis was based on 18 clinical RCTs including 777 patients with CHF. We found that FES had considerably improved peak VO_2, 6MWD, and MHFLQ of HF patients

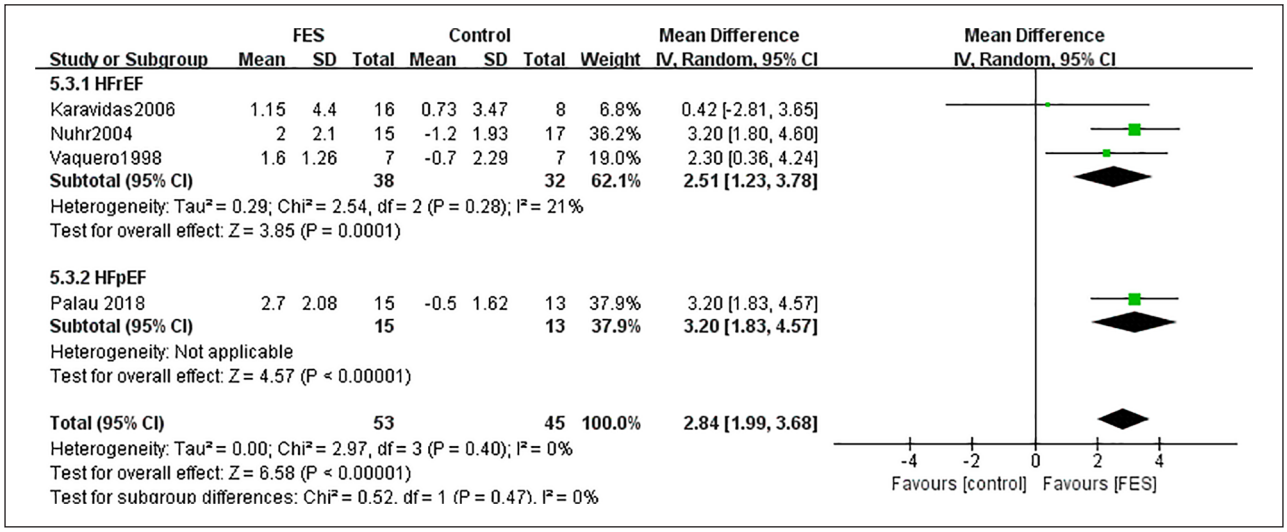

Figure 2. Forest plot of the effects of functional electrical stimulation of the legs on peak oxygen consumption of FES versus control.

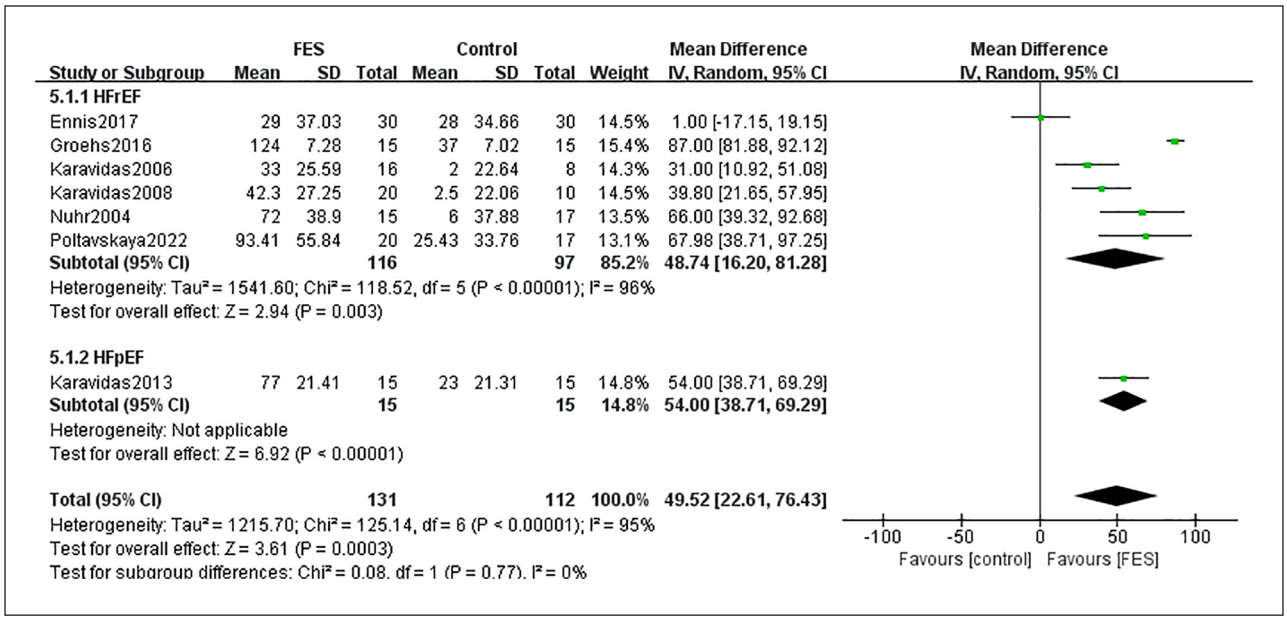

Figure 3. Forest plot of the effects of functional electrical stimulation of the legs on 6-min walking distance of FES versus control.

when compared to the placebo control. Traditional exercise rehabilitation therapy was more successful in improving peak VO_2, 6WMD, and QoL than FES, especially for patients with HFrEF. In patients with HFpEF, FES did not show a significant difference compared to standard exercise rehabilitation therapy concerning peak VO_2 and QoL improvement. However, according to our study, we found that FES is more convenient because it can be done at home independently. Furthermore, a positive correlation was observed between the frequency of electrical stimulation and the treatment outcome, indicating that higher frequencies yielded better results, as long as patient safety was upheld. Ennis previously conducted a low-frequency electrical stimulation that remained at 4–5 Hz.[25] We compared this study with other studies that conducted relatively high-frequency electrical stimulation, demonstrating that the effectiveness of FES is related with its frequency. This might be the reason that some results appeared with high heterogeneity. Considering that only one article is available about the low-frequency FES, subgroup analysis was not conducted.

Despite the considerable progress in CHF treatment, the 5-year survival rate of patients with CHF remains lower than those with most malignancies.[5] Furthermore, exercise intolerance, lower capacity of aerobic exercise, and decreased QoL in patients with advanced CHF impose huge financial costs on the patients and the society. The classification of

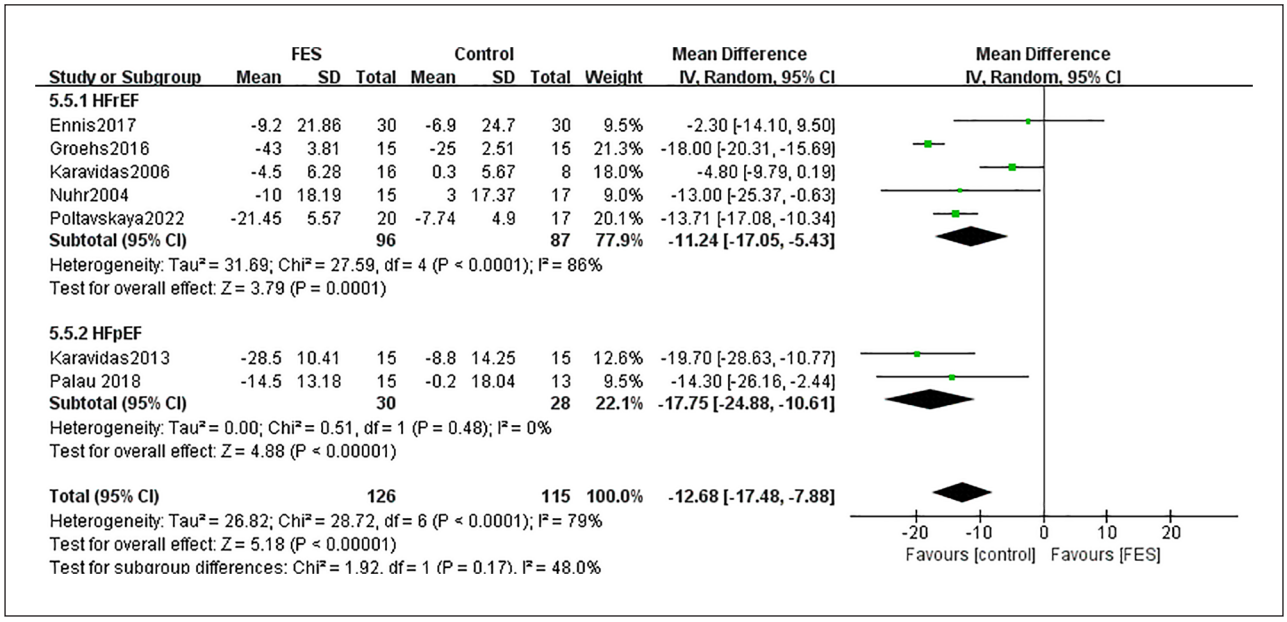

Figure 4. Forest plot of the effects of functional electrical stimulation of the legs on Minnesota living with heart failure questionnaire scores of FES versus control.

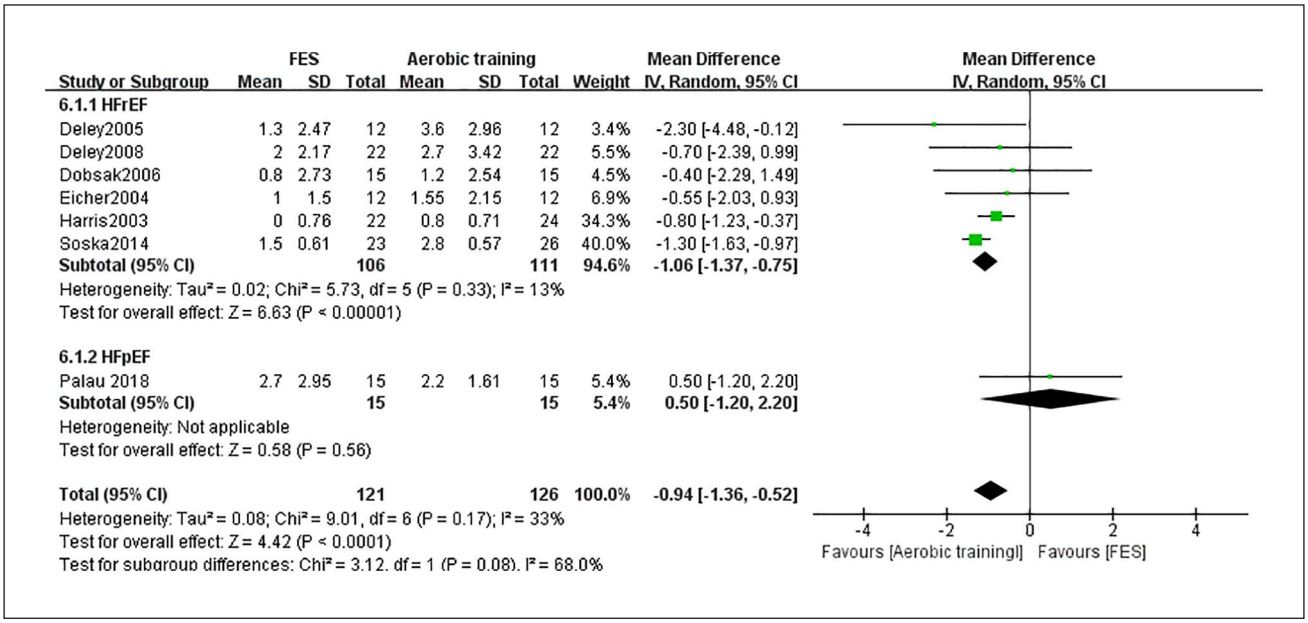

Figure 5. Forest plot of the effects of functional electrical stimulation of the legs on peak oxygen consumption of FES versus cycle.

CHF is divided into three categories based on different LVEF (left ventricle ejection fraction): LVEF of HFrEF ⩽ 40%, LVEF of HF with moderate ejection fraction (HFmrEF): 41%–49%, LVEF of HFpEF ⩾ 50%, according to the 2021 guidelines.[6] Approximately 1 million individuals are hospitalized due to CHF in the United States, and among these cases, about half are attributed to HFrEF.[2] Patients with HFrEF were the major focus of the studies included in this meta-analysis. As a result, this study has a greater clinical value to manage the prognosis of patients with HFrEF.

FES has been shown to improve peak VO_2 in patients by activating skeletal muscle,[3] potentially enhancing their leg muscle strength, inhibiting sympathetic activity, reducing levels of inflammatory factors, aerobic and oxidative energy

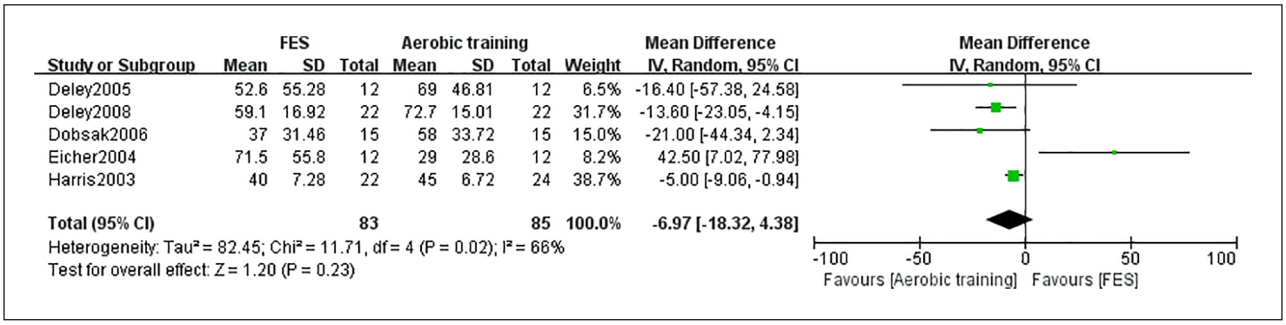

Figure 6. Forest plot of the effects of functional electrical stimulation of the legs on 6-min walking distance of FES versus cycle.

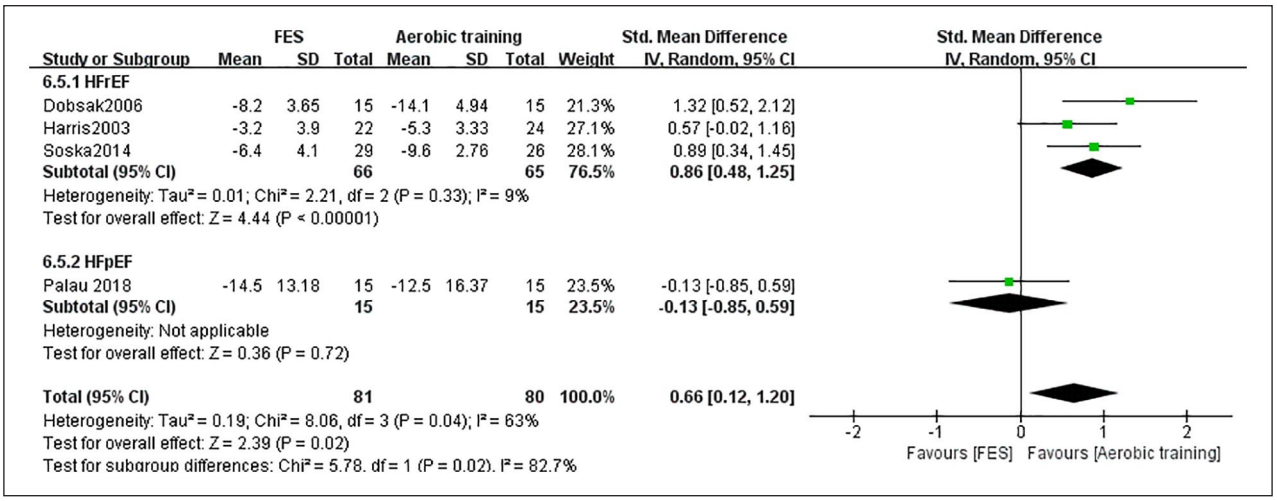

Figure 7. Forest plot of the effects of functional electrical stimulation of the legs on Minnesota living with heart failure questionnaire scores of FES versus cycle.

metabolism and depression rates, and possibly improving endothelial functions.[28] In addition, 6WMD, a predictor of CHF, can improve the QoL of patients with CHF.[7]

Exercise has been shown to be beneficial in preventing HF development (primary prevention). Individuals who met the guideline-recommended minimum exercise threshold of 500 METs-min/work were 10% less likely to develop CHF than those not engaged in physical activity.[29] Another study also demonstrated that regular exercise could effectively prevent CHF.[30] For patients who had already experienced CHF, exercise training could reduce the mortality and hospitalization rates.[31] As a result, according to the European Society of Cardiology CHF guideline 2016, patients with CHF should be advised to undergo appropriately designed exercise training even if their ejection fraction is lowered.[32] However, barely 10% of the eligible patients hospitalized for CHF received exercise program instruction. This could be due to the patients' health condition and the degree of difficulty at which exercise therapy could be implemented.[33] Therefore, exercise might not be widely recommended for patients with CHF, and FES, serving as an alternative therapy for CHF patients who cannot or choose not to exercise, has emerged as a significant component of future anti-HF therapies. FES has higher convenience than exercise training because patients can perform it at home with prior guidance. According to the collected data, higher FES frequency resulted in better treatment effects. Currently, besides potential muscle soreness in some individuals, no other side effects have been reported associated with FES therapy (Supplemental Table 2).

FES, which uses electrical stimulation to induce muscular contractions, has been proven to improve CHF prognosis by enhancing endothelial function[23] and lowering sympathetic nerve activity.[24] Endothelial dysfunction is one of the key mechanisms of cardiovascular diseases and atherosclerosis. Flow-mediated dilatation (FMD) is an important mechanism of vasodilation that controls vascular tone and peripheral circulatory homeostasis. It occurs in virtually every vascular bed within the body. FMD can be endothelium dependent and is triggered when arteries are exposed to increased flow and shear stress. This mechanism causes the blood vessels to dilate in response to elevated blood flow passing through them. Endothelial dysfunction is reflected by an impaired/attenuated response to FMD.[34] In older adults, reduced physical activity can exacerbate this dysfunction. This condition arises from decreased expression and function of endothelial

nitric oxide synthase, which accelerates the breakdown of nitric oxide and the generation of reactive oxygen species. FES has been shown in previous studies to assist with FMD. Overactive sympathetic nerves are a characteristic feature of CHF, and they directly influence the onset and progression of CHF.[35] Muscle sympathetic nerve activity (MSNA) has been demonstrated with independent prognostic value in patients with CHF and to better predict mortality metrics. As a result, lowering MSNA is a primary target of CHF interventions. A negative connection between changes in MSNA and exercise ability was reported by a study about cycling in middle-aged individuals with or without HFrEF. This study provided support for the potential role of exercise training in reducing sympathetic activity in high-risk individuals, as suggested by previous research.[36] According to Notarius et al., FES can lower MSNA.

Study limitation

Certain limitations were associated with this study. The studies considered were small in sizes and had relatively short durations, spanning only a few weeks. Due to this limited time frame, crucial endpoints such as mortality and CHF-related re-hospitalization could not be evaluated adequately based on insufficient data availability. Furthermore, this study did not focus on patients with higher NYHA classes, due to the scarcity of research, it was impossible to ascertain whether FES could improve the NYHA classes and LVEF of the patients. If focus were directed toward CHF patients who were unable to engage in exercise training initially, it could help establish criteria for transitioning from exercise training to FES.

Conclusion

Compared with placebo group, FES is beneficial for patients with moderate to severe CHF. For patients with HFrEF, aerobic exercise works better. Therefore, aerobic exercise is preferred for the patients capable of engaging in exercise, while FES is recommended for those unable to actively exercise. While prioritizing patient safety, higher frequencies of current stimulation and longer cumulative time tend to yield more favorable effects.

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None.

Authors' contributions

JC designed and conducted the research; RZ, JC, and YW collected data; RZ analyzed the data and constructed the initial manuscript draft; JC revised the manuscript; QL and RZ finalized the manuscript. The final version of the manuscript was read and approved by all authors.

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of conflicting interests

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Informed consent

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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