Functional electrical stimulation of peripheral muscles improves endothelial function and clinical and emotional status in heart failure patients with preserved left ventricular ejection fraction

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Background Functional electrical stimulation (FES) improves exercise capacity, quality of life, emotional stress, and endothelial function in chronic heart failure with impaired systolic function. We sought to investigate the effects of FES on the above parameters in patients with preserved ejection fraction (HFpEF).

Methods Thirty HFpEF patients, 18 female and 12 male, aged 69 ± 8 years, in New York Heart Association class II or III and with mean ejection fraction 63% ± 6%, were randomly (1:1) assigned to a 6-week FES program or placebo. Assessment was performed at baseline and after completion of training protocol and included 6-minute walked distance, quality of life (Kansas City Cardiomyopathy Questionnaire and Minnesota Living with Heart Failure Questionnaire), depressive symptoms (Beck Depression Inventory and Zung self-rated depression scores), B-type natriuretic peptide, endothelial function (flow-mediated dilatation), and left ventricular diastolic function.

Results A significant improvement in 6-minute walked distance (F = 21.61, *P* = .001), Kansas City Cardiomyopathy Questionnaire summary (F = 8.68, *P* = .006), Minnesota Living with Heart Failure Questionnaire (F = 6.43, *P* = .017), Beck Depression Inventory (F = 6.66, *P* = .015), Zung (F = 6.25, *P* = .019), and flow-mediated dilatation diameter (F = 11.98, *P* = .002) was observed in the FES group compared with placebo group; B-type natriuretic peptide also declined but not significantly (F = 0.249, *P* = .622), and there was a tendency toward lower mitral E/e' wave ratio (F = 3.066, *P* = .091).

Conclusion As in heart failure and reduced left ventricular ejection fraction, FES also improves exercise capacity, quality of life, emotional status, and endothelial function in HFpEF. Given the lack of effective evidence-based therapies in these patients, FES warrants further investigation. (Am Heart J 2013;166:760-7.)

The recently published European Society of Cardiology Guidelines for heart failure recommends aerobic exercise training to all stable chronic heart failure patients to improve functional capacity and symptoms.[1] Indeed, increasing evidence suggests that, in patients with chronic heart failure and reduced left ventricular (LV) ejection fraction (HFrEF), exercise training improves clinical status and may also improve long-term outcome.[2] Functional electrical stimulation (FES) of the lower limbs, as an alternative to physical training, also improves muscle performance, exercise capacity, endothelial function, quality of life, and emotional stress in HFrEF.[3-7]

More than 50% of patients with symptomatic heart failure have preserved LV ejection fraction (HFpEF),[8-10] and their morbidity and mortality rates are high and comparable with those of HFrEF.[9] In these patients, however, there is a considerable lack of effective evidence-based therapies, as several medical modalities established in HFrEF failed to show improvement in long-term prognosis.[1] Because the adherence of heart failure patients to traditional exercise training programs remains well below the recommended levels[11] and, to our knowledge, there are no published data regarding the use of FES in HFpEF patients, we sought to evaluate the effects of this treatment modality on clinical and

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RCT number NCT01829607.
Submitted February 27, 2013; accepted June 29, 2013.

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0002-8703/$ - see front matter

http://dx.doi.org/10.1016/j.ahj.2013.06.021

emotional status, endothelial function, and LV diastolic function in this specific patient population.

Methods

Study population

A total of 30 consecutive patients, 18 female and 12 male, with chronic HFpEF, followed in the heart failure outpatient clinic of our department, were enrolled over a 6-month period. Based on the recommendation of the European Society of Cardiology, the inclusion criteria were as follows: (i) symptoms (New York Heart Association [NYHA] class II or III) and signs typical of heart failure, (ii) LV ejection fraction >50% and LV end-diastolic volume index <97 mL/m^2, (iii) findings of left atrial (LA) dilatation (LA volume index >40 mL/m^2), LV hypertrophy and/or LV diastolic dysfunction (ie, mitral E/A ratio <1 or >2, mitral E/e' ratio >15 or 8-15 [A pulmonary − A mitral] duration difference >30 ms etc), (iv) no alterations in medical therapy during the previous 4 weeks, and (v) no myocardial infarction within 3 months before enrollment.[1,10] Exclusion criteria included recent (≤4 weeks) heart failure decompensation, acute coronary syndrome, chronic inflammatory diseases, and malignancies.

Study protocol

The study protocol was approved by the institute's ethics committee, and all patients gave written informed consent. Patients were randomly assigned (1:1) to a 6-week FES training program or a placebo training program. Training was performed at the physiotherapy department of our institution, under the supervision of a chief therapist. Eight adhesive electrodes (size, 50 × 90 mm) were positioned on the skin over the upper lateral and lower medial aspects of the quadriceps muscle of both legs and over the upper and lower portions of the gastrocnemius muscles of both legs. On the quadriceps of both legs, the upper electrode was positioned 4 cm below the inguinal fold, whereas the lower electrode was placed above the kneecap. On the gastrocnemius, the upper electrode was positioned 2 cm below the popliteal fossa, whereas the lower was placed just above the Achilles tendon of both tibials. In the FES group, the stimulator was configured to deliver a direct electrical current at 25 Hz for 5 seconds followed by a 5-second rest. The intensity of the stimulation was adjusted to achieve a visible muscle contraction that was not sufficiently strong to cause discomfort or a significant movement at either the knee or the ankle joints. When the muscles of the right leg were contracted, the muscles of the left leg were relaxing and vice versa. The patients were trained for 30 minutes a day, 5 days per week for a total of 6 weeks. The placebo group was exposed to the same regimen as the FES group, using a lower intensity of stimulation (5 Hz) that did not lead to visible or palpable contractions, as judged objectively or subjectively.

Patient assessment was performed before and after completion of the FES or placebo training protocol. The primary end point of the study was the effect of FES on endothelial function, as evaluated by the change in brachial artery flow-mediated dilation (FMD). Secondary end points were exploratory and included exercise capacity, quality of life, depressive symptoms, natriuretic peptides, and LV diastolic function.

Six-minute walked distance (6MWD), as an index of exercise capacity, was performed in a properly graded (every 20 m) corridor of our heart failure clinic, under the supervision of a physician who was blinded to the treatment status of each patient.

Table I. Baseline characteristics of the 2 treatment groups

	FES (n = 15)	Placebo (n = 15)	*P*
Demographics			
Age (y)	69.4 ± 8.6	68.5 ± 7.9	.778
Gender (male/female)	6/9	6/9	1.000
History			
Diabetes mellitus (%)	8 (53.3)	6 (40)	.464
Arterial hypertension (%)	15 (100)	15 (100)	NA
Hypercholesterolemia (%)	8 (53.3)	12 (80)	.121
Smokers (%)	1 (6.7)	3 (20)	.283
Atrial fibrillation (%)	6 (40)	6 (40)	1.000
Functional status			
NYHA class, II/III (%)	11/4 (73.3/26.7)	10/5 (66.7/33.3)	.690
6-min walked distance (m)	324 ± 54	322 ± 76	.917
Quality of life and emotional status			
KCCQ summary	34 ± 12	31 ± 8	.508
KCCQ functional	39 ± 7	39 ± 7	.741
MLHFQ	45.6 ± 12.9	46.7 ± 17.5	.851
BDI	11.2 ± 6.2	12.1 ± 4.3	.663
Zung SDS	42.3 ± 8.4	38.6 ± 6.2	.188
Main laboratory findings			
Hematocrit (%)	40.1 ± 2.3	40.13 ± 2.64	.930
Urea (mg/dL)	46.0 ± 10.2	55.2 ± 33.8	.322
Creatinine (mg/dL)	1.2 ± 0.3	1.4 ± 0.9	.334
BNP (pg/mL)	646 ± 188	668 ± 209	.772
Endothelial function			
Brachial artery FMD (%)	5.3 ± 3.0	3.8 ± 2.0	.128
Echocardiography			
IVS (cm)	1.2 ± 0.1	1.2 ± 0.1	.800
PW (cm)	1.1 ± 0.1	1.1 ± 0.1	.290
LV ejection fraction (%)	63.6 ± 7.6	62.6 ± 4.5	.668
LA volume (mL)	57.6 ± 15.3	60.7 ± 10.8	.523
Mitral E wave (m/s)	0.7 ± 0.3	0.8 ± 0.3	.855
Mitral A wave (m/s)	0.8 ± 0.1	0.8 ± 0.1	.401
Mitral E/A ratio	0.7 ± 0.4	0.6 ± 0.1	.542
Mitral deceleration time (ms)	255.5 ± 67.9	234.0 ± 62.9	.377
Mitral E/e' ratio	11.1 ± 2.5	11.2 ± 2.4	.942
(A pulm – A mitral) duration (ms)	25.1 ± 4.5	26.2 ± 5.3	.644

NA, Nonapplicable; *IVS*, intraventricular septum thickness; *PWT*, LV posterior wall thickness; *RV*, right ventricular; *E*, early diastolic mitral inflow wave; *A*, late diastolic mitral inflow wave; *e'*, early diastolic velocity of mitral annulus; (A pulm – A mitral) duration, time difference between pulmonary vein flow A-wave duration and mitral flow A-wave duration.

Assessment of quality of life and screening for depressive symptoms and emotional stress was performed using standard questionnaires and more specifically the Kansas City Cardiomyopathy Questionnaire (KCCQ), the Minnesota Living With Heart Failure Questionnaire (MLHFQ), the Beck Depression Inventory (BDI), and the Zung self-rating depression scale (SDS).[12-16]

Plasma B-type natriuretic peptide (BNP) levels were measured by standard immunoassay technique (Triage BNP assay; Biosite, Inc, San Diego, CA).

Endothelial function was assessed by a high-resolution ultrasound system (Philips HDI 5000 Sonos CT, Philips Healthcare, Best, The Netherlands) and an 8-MHz linear array

Table II. Mean values ± SD of study parameters at baseline (before) and at the end of the study protocol (after) along with the corresponding changes (SE) in the 2 study groups

	FES (n = 15)			Placebo (n = 15)				
	Before	After	Change (SE)	Before	After	Change	F statistic*	P*
6-min walked distance (m)	324 ± 54	401 ± 67	76.33 (6.90)	322 ± 76	345 ± 74	23.53 (8.96)	21.61	.001
KCCQ summary	34 ± 12	47 ± 15	13.0 (4.0)	31 ± 8	37 ± 10	5.0 (2.0)	8.68	.006
KCCQ functional	39 ± 7	53 ± 6	14.0 (2.0)	39 ± 7	44 ± 8	5.0 (2.0)	6.81	.014
MLHFQ	45.6 ± 12.9	17.1 ± 11.9	−28.46 (3.50)	46.7 ± 17.5	37.9 ± 16.5	−8.73 (5.60)	6.43	.017
BDI	11.2 ± 6.2	6.1 ± 4.4	−5.13 (1.20)	12.1 ± 4.3	10.7 ± 3.4	−1.40 (0.76)	6.66	.015
Zung SDS	42.3 ± 8.4	32.4 ± 8.7	−9.86 (2.20)	38.6 ± 6.2	37.0 ± 6.6	−1.60 (2.42)	6.25	.019
BNP (pg/mL)	646 ± 188	291 ± 99	−355 (157)	668 ± 209	320 ± 100	−347 (36)	0.25	.622
Brachial artery FMD (%)	5.3 ± 3.0	9.2 ± 3.9	3.0 (1.0)	3.8 ± 2.0	4.1±1.6	0.2 (1.0)	11.98	.002
LA volume (mL)	57.6 ± 15.3	55.0 ± 15.8	−2.53 (0.81)	60.7 ± 10.8	60.5 ± 10.8	−0.20 (0.32)	0.78	.386
Mitral E wave (m/s)	0.7 ± 0.3	0.7 ± 0.2	−0.09 (0.04)	0.8 ± 0.3	0.7 ± 0.2	−0.05 (0.02)	0.16	.691
Mitral A wave (m/s)	0.8 ± 0.1	0.8 ± 0.2	0.01 (0.04)	0.8 ± 0.1	0.8 ± 0.1	−0.06 (0.03)	0.21	.656
Mitral E/A ratio	0.7 ± 0.4	0.6 ± 0.1	−0.08 (0.13)	0.6 ± 0.1	0.7 ± 0.1	0.04 (0.03)	0.12	.735
Mitral E/e' ratio	11.1 ± 2.5	7.6 ± 1.6	−3.25 (0.45)	11.2 ± 2.4	9.1 ± 1.9	−2.06 (0.49)	3.07	.091
(A pulm − A mitral) duration (ms)	25.1 ± 4.5	19.0 ± 7.2	−6.11 (2.73)	26.2 ± 5.3	18.8 ± 4.1	−7.33 (2.80)	0.09	.771

* Analysis of variance for repeated measures.

transducer. Endothelium-dependent brachial artery FMD, endothelium-independent nitroglycerin-mediated vasodilation, and Doppler velocity measurements (hyperemic flow) of the conduit brachial artery were determined as previously described.[4]

Cardiac geometry and function were assessed by 2-dimensional transthoracic echocardiography using standard methodology. All echocardiograms were performed by a specialist blinded to the treatment status of each patient, using an iE33 xMATRIX Phillips system (Royal Philips Electronics, Amsterdam, The Netherlands) with a 2.5-MHz transducer.

Statistical analysis

Sample size calculation was based on previous data concerning the primary end point, according to which the mean ± SD of FMD was 5.2% ± 2.4%.[17] A sample size of 15 per group (30 in total) has a 90% power to detect an effect size of 0.8 (Cohen's *d*) in a design with 2 repeated measurements when the SD is 2.4, the correlation ρ between baseline and second measurement is 0.7, and the α level is .05. Categorical variables are expressed as percentages of the corresponding population and were compared using the χ^2 test. Continuous variables are expressed as mean ± SD and were compared using the Student *t* test for independent and paired samples or the Mann-Whitney *U* test and Wilcoxon signed rank test, according to whether variables followed a normal distribution, as assessed by the Kolmogorov-Smirnov test. Analysis of variance (ANOVA) for repeated measurements with treatment arm as a covariate (2-way ANOVA) was used to assess the effect of treatment; results for each variable tested are reported as mean difference, SE of the difference, F-statistic (weigh of interaction with treatment), and *P* value; results were provided by the Sphericity test or the Greenhouse-Geisser test in case the criteria for sphericity were not met. For the primary end point, we performed multivariate adjustment for covariates that might have a confounding role on the relationship of FES with FMD including age, gender, hypercholesterolemia, diabetes mellitus, and smoking status. For the secondary end points, we did not perform any adjustment because these end points were exploratory. $P < .05$ was considered statistically significant. Statistical analysis was performed using the SPSS 13.0 statistical software package (SPSS, Inc, Chicago, IL).

No extramural funding was used to support this work.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Results

Patients' clinical characteristics at baseline are summarized in Table I. No significant differences were observed between the 2 study groups in baseline parameters (all $P > .05$). The effect of FES and placebo on study parameters is shown in Table II.

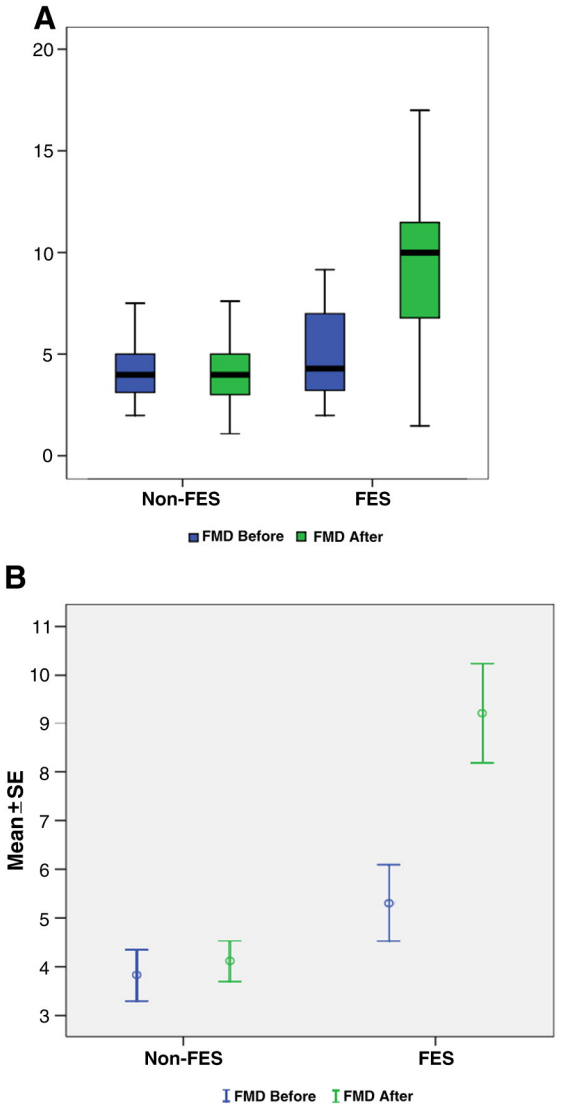
Endothelial function

The baseline FMD did not differed between FES and non-FES group (5.3% ± 3% vs 3.8% ± 2%, $P = .128$, respectively, Table I). We observed that patients who completed FES had an increase in FMD (5.3% ± 3% vs 9.2% ± 3.9%, $P < .001$). However, patients who underwent the placebo training protocol had no change in FMD at a statistical significant level (3.8% ± 2% vs 4.1% ± 1.6%, $P = .495$). Repeated-measurements ANOVA revealed a statistical significant increase in FMD in the FES group compared with the non-FES group ($P = .002$, Figure 1A and B); this difference remained significant after adjustment for several confounders including age, gender, hypercholesterolemia, diabetes mellitus, and smoking status ($P = .001$).

Exercise capacity

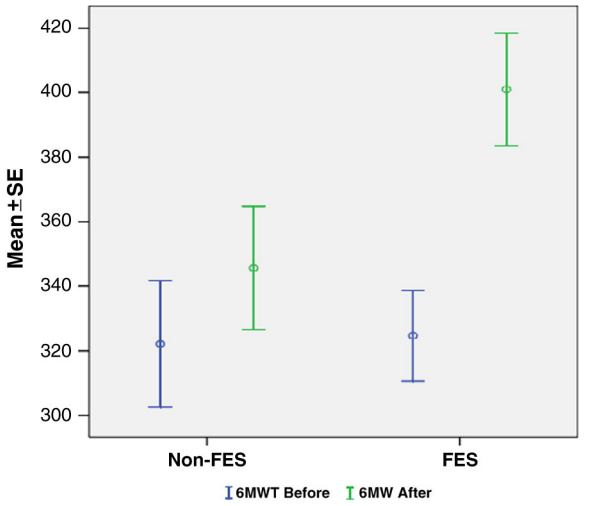
Patients in the FES group had a significant increase in 6-minute walked distance (324 ± 54 vs 401 ± 67, $P < .001$, ANOVA for repeated measures: $P < .001$) (Figure 2).

Figure 1



Box plot (**A**) and error bar charts (**B**) (mean ± SE) of FMD (%) in the study groups.

Figure 2



Error bar charts (mean ± SE) of 6-minute walk test (6MWT) in the study groups.

Quality of life

The KCCQ functional, KCCQ summary, and MLHFQ scores improved significantly in the FES group (39 ± 7 vs 53 ± 6, $P < .001$, 34 ± 12 vs 47 ± 15, $P = .002$, and 45.6 ± 12.9 vs 17.1 ± 11.9, $P < .001$, respectively, ANOVA for repeated measures: KCCQ functional $P = .018$, KCCQ summary $P = .006$, MLHFQ $P = .017$) (Figure 3A-C).

Depressive symptoms

A significant amelioration following FES therapy was also observed in both questionnaires screening for depressive symptoms, that is, BDI and Zung self-rated depression scores (11.2 ± 6.2 vs 6.1 ± 4.4, $P = .001$, and 42.3 ± 8.4 vs 32.4 ± 8.7, $P = .001$, ANOVA for repeated measures: BDI, $P = .015$, and Zung, $P = .019$) (Figure 4A and B).

Echocardiographic evaluation of LV diastolic function

A tendency toward a lower mitral E/e' wave ratio was observed in the FES group (ANOVA for repeated measures, $P = .091$). None of the other echocardiographic indices were statistical significantly affected by the intervention (all $P > .05$).

B-type natriuretic peptide levels

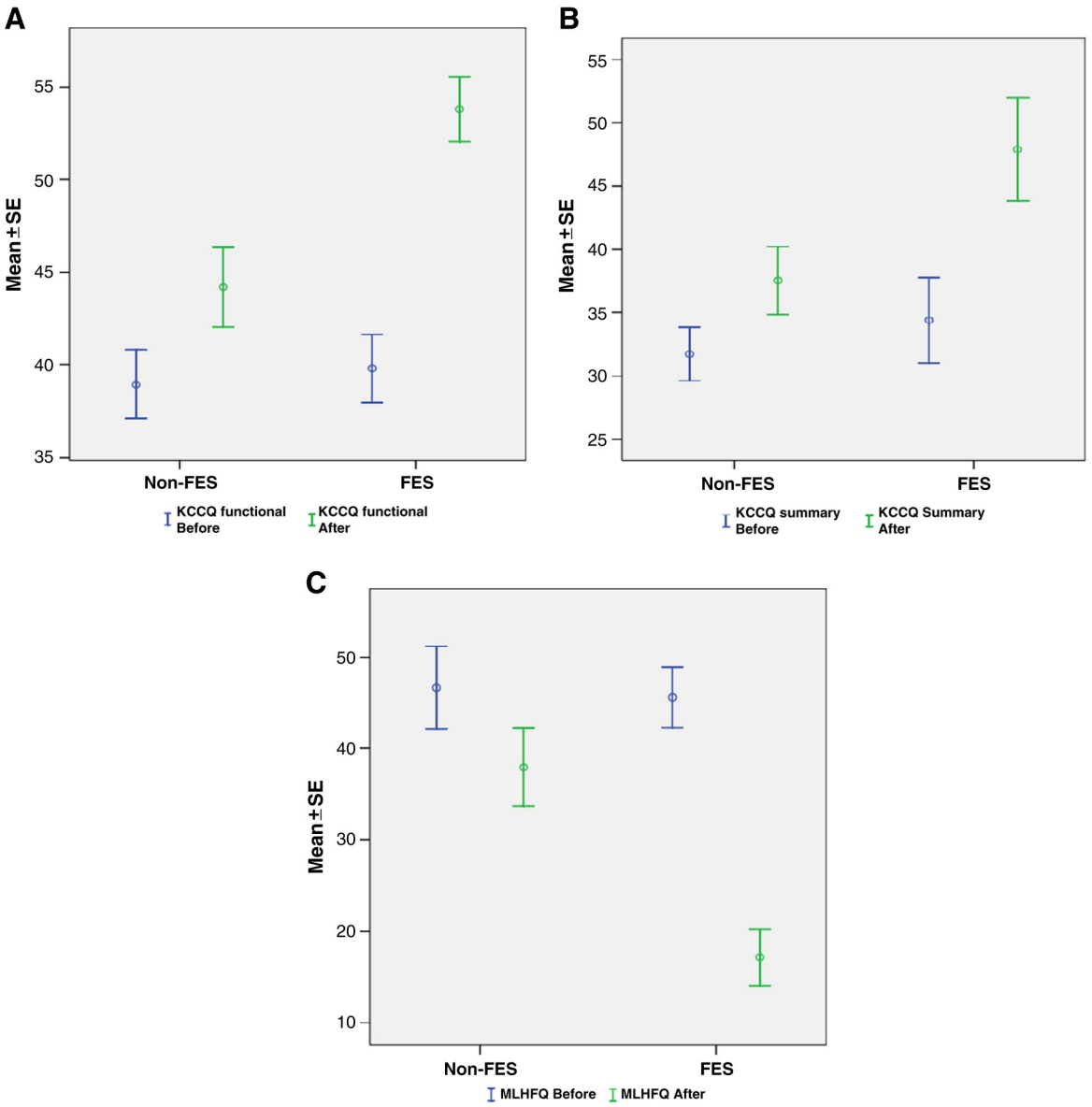
A nonsignificant change in plasma BNP levels was observed between both groups (ANOVA for repeated measures, $P = .622$).

Discussion

In this first study of FES in patients with HFpEF, a 6-week FES program applied on lower limbs improved exercise capacity, quality of life, and emotional status with a parallel improvement in endothelial function, whereas BNP levels and LV diastolic function indices were not significantly affected.

Exercise training has been found to improve exercise capacity in HFrEF, an effect that is mediated by cardiac and extracardiac mechanisms.[18-23] Of particular interest, exercise training was able to reduce diastolic stiffness in patients with HFrEF.[24] In addition, a recently published meta-analysis showed that FES, although inferior to

Figure 3

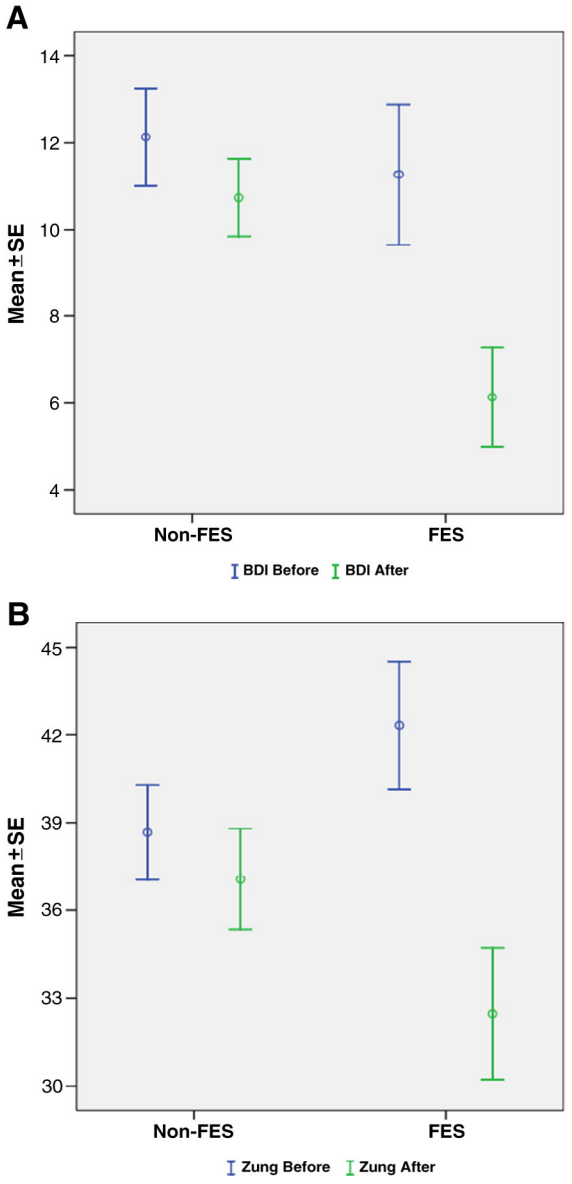


Error bar charts (mean ± SE) of KCCQ functional (**A**), KCCQ summary (**B**), and MLHFQ (**C**) in the study groups.

traditional exercise training programs, produced significant improvement in HFrEF patients as far as fitness and quality of life was concerned.[25] These observations, together with promising, albeit preliminary, evidence concerning the beneficial effects of exercise training in patients with HFpEF, gave the rationale for the present study, which demonstrated, to our knowledge for the first time, that FES of the lower limb muscles improved functional capacity along with endothelial function in this patient population, whereas these beneficial effects paralleled the significant improvement in patients' quality of life and emotional stress.

A cardinal feature of heart failure, irrespectively of ejection fraction, is exercise intolerance, which is strongly associated with quality of life and clinical outcomes.[26] A recent meta-analysis showed that exercise training improves exercise capacity and quality of life in HFpEF.[27] According to our finding, FES, an alternative to exercise training, increased the distance covered during the 6-minute walk test, with a parallel improvement in quality of life and depression scales. The FES-induced beneficial changes in peripheral hemodynamics and skeletal muscle metabolic status, the reversion of a "deconditioning" process that is common in sedentary

Figure 4



Error bar charts (mean ± SE) of BDI (**A**) and Zung self-rated depression (**B**) scores in the study groups.

patients with heart failure, and the counteraction of the vicious cycle mobilized by activated neurohormonal and inflammatory pathways are potential mechanisms that could explain the favorable outcomes in functional capacity and quality of life of patients with HFpEF. Decreased exercise capacity, on the other hand, is a main factor restricting everyday life of congestive heart failure (CHF) patients, thus compromising their quality of life. The improved exercise capacity contributes to the general well-being of these patients in their daily activities, and this fact may beneficially affect their quality of life.[28] The FES-induced favorable effect on KCCQ and MLHFQ scores may also have prognostic implications in HFpEF patients because these scales have been associated with adverse clinical outcomes and their improvement by therapeutic interventions may predict lower rehospitalization rates.[29]

Moreover, FES improved depression symptoms in HFpEF patients, providing an additional clinical advantage because emotional stress has been shown to adversely affect both short- and long-term prognosis in CHF patients.[30] The prevalence of depression in hospitalized CHF patients ranges from 35% to 70%, and depressive symptoms are associated with a significant increase in the risk of both mortality and readmission rate of these patients.[31-33] In this study, we assessed emotional stress using instruments that screen somatic and nonsomatic depressive symptoms, which have been validated in the Greek language, focusing for the first time on the impact of FES on the emotional status of HFpEF patients. The FES-induced improvement in exercise capacity and functional status, the favorable effect on the patients' general well-being, and their quality of life as well as the alleviation of the numerous daily activity limitations experienced by these patients are some of the probable reasons for the beneficial effect exerted on the patients' emotional status. A number of studies have shown that running induces neurochemical and morphological adaptations in brain reward pathways that account for its antidepressive effect.[1,34,35] Functional electrical stimulation of peripheral muscles could constitute an alternative means of inducing these beneficial neurochemical and morphological effects in the brain, but further studies are needed in this area.

One of the factors that may contribute to HFpEF pathophysiology is the abnormal ventriculoarterial interaction due to the stiffening of both systems.[36] Vascular stiffness rises with age and hypertension, which are both common features of HFpEF patients.[37] Gregory et al[38] reported reduced aortic distensibility in HFpEF beyond that predicted by age that correlated with exercise intolerance. On the other hand, LV stiffness also rises with age, and combined with arterial stiffening, it may greatly amplify the effects of even small changes in blood volume on arterial pressure and cardiac workload.[37,39] Systolic ventricular and arterial stiffening could influence diastole by elevating systolic load to prolong relaxation, compromise filling, and raise end-diastolic pressure. Thus, the amelioration of endothelial function following FES therapy may have beneficial effects in ventriculoarterial interaction and thus cardiac function.

Some previous studies have shown that exercise training programs enhance diastolic function reserve through an improvement in muscle performance, endothelial function, and neurohormonal profile.[24,25,40-43] However, in a recent meta-analysis of 5 trials of exercise training in HFpEF, none of the trials showed an improvement in

mitral E/A ratio, whereas only one of them showed a decrease in E/e' ratio.[27] We only found a FES-induced nonsignificant trend for E/e' ratio decrease, whereas no other LV diastolic function index was significantly affected and the same applied to BNP levels. The form and the duration of the applied training programs may account, at least in part, for such discrepancies. The BNP change, in particular, was a secondary exploratory end point, and therefore, this study was not powered to assess it. Moreover, FES seems to act primarily on peripheral vascular system, as documented by the significant FMD improvement, whereas its effects on central cardiac function may be indirect and thus without a significant impact on BNP. Finally, BNP has a relatively short half-life and, therefore, is more suitable for detecting short-term changes in ventricular wall stress, whereas the effects on exercise capacity, quality of life, and emotional status were progressive and long lasting, as detected by the corresponding variables. The nonsignificant decline of BNP coincides with the nonsignificant decrease of E/e' ratio, also observed herein.

In conclusion, the present study demonstrated that FES of lower limbs improves endothelial function along with clinical and emotional status in patients with HFpEF offering a potential therapeutic modality for this particular population characterized by a hitherto lack of proven therapies.[3-7] The small sample size is an obvious limitation of this study, and the promising preliminary findings observed herein warrant further evaluation in larger patient populations as well as longer exercise periods.

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