

# Low frequency electrical muscle stimulation and endothelial function in advanced heart failure patients

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## Abstract

**Aim** Obtain initial estimates of the change in brachial artery endothelial function and maximal oxygen uptake ( $VO_{2peak}$ ) with 8 weeks of low-frequency electrical muscle stimulation (LF-EMS) or sham in patients with advanced chronic heart failure.

**Methods and results** Using a double blind, randomized design, 35 patients with chronic heart failure (New York Heart Association class III–IV) were assigned to 8 weeks (5 × 60 min per week) of either LF-EMS (4 Hz, continuous) or sham (skin level stimulation only) of the quadriceps and hamstrings muscles. Four of the five sessions were at home and one under supervision. Ultrasound images of resting brachial artery diameter and post 5 min occlusion to determine flow-mediated dilation (FMD), a marker of vascular function and peak oxygen uptake ( $VO_{2peak}$ ) during cardiopulmonary exercise test, were measured before and after LF-EMS ( $n = 20$ ) and sham ( $n = 15$ ) interventions. FMD improved by 2.56% (95% confidence interval: 0.69 to 3.80) with LF-EMS compared with sham ( $P = 0.07$ ). There were no notable changes in  $VO_{2peak}$ .

**Conclusions** Improvements in FMD with LF-EMS may have a clinically meaningful effect as higher FMD is associated with better prognosis. This is a preliminary finding, and a larger trial is warranted.

**Keywords** Advanced heart failure; Cardiac rehabilitation; Endothelial function electrical muscle stimulation; Neuromuscular electrical stimulation; Flow-mediated dilation

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## Introduction

New York Heart Association (NYHA) class III/IV chronic heart failure (CHF) patients are unable to perform simple activities of daily living.<sup>1</sup> Low fitness<sup>2</sup> and endothelial dysfunction<sup>3</sup> are predictors of mortality in CHF and are useful targets for treatment. Low-frequency electrical muscle stimulation (LF-EMS) has been explored as a potential therapy in patients with mild CHF with positive outcomes.<sup>4–6</sup> Improvements in exercise capacity and endothelial function with LF-EMS in patients with CHF NYHA class III/IV could reduce the incidence of all-cause mortality<sup>7</sup> and improve overall quality of life. We have reported previously that a randomized control trial is feasible in this patient group, but minimal improvements in quality of life and functional capacity were evident.<sup>8</sup> Here, we aimed to obtain initial

estimates of the change in brachial artery endothelial function and maximal oxygen uptake ( $VO_{2peak}$ ) with LF-EMS in a subset of patients with CHF class III/IV from our larger feasibility trial.<sup>8</sup> We hypothesized that 8 weeks of LF-EMS would enhance endothelial function and cardiorespiratory fitness.

## Methods

### Research design

Fifty-six participants with stable CHF NYHA functional class III–IV symptoms (ejection fraction <40% on echocardiography, *Table 1*) were randomized to either LF-EMS

( $n = 28$ ) or 'sham' placebo ( $n = 28$ ) for a period of 8 weeks in a double blind, parallel group, randomized controlled feasibility trial, which is reported elsewhere.<sup>8</sup> A subset of participants (LF-EMS  $n = 20$ , sham  $n = 15$ , *Figure 1*) from the original trial were able to tolerate the additional research measurement (withdrawn,  $n = 10$ ; unable to tolerate tests,  $n = 5$ ; refused tests due to illness,  $n = 6$ ) and underwent assessment of endothelial function and maximal oxygen uptake. Participants with implantable cardiac devices, life-threatening cardiac arrhythmias, neurological disorders, or previous stroke were excluded. The study received ethical approval and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

### Low-frequency electrical muscle stimulation/sham stimulation

Detailed description of the LF-EMS and sham interventions is described previously.<sup>8</sup> Briefly, the LF-EMS equipment (Biomedical Research Limited, Galway, Ireland) containing built-in adhesive gel electrodes was worn on the upper legs. The LF-EMS group received stimulation at a pulse frequency of 4 Hz (pulse width: 620  $\mu$ s, maximum current

amplitude: 140 mA). The sham group received a very low level of stimulation (frequency: 99 Hz, pulse width: 150  $\mu$ s, maximum current amplitude: 7.3 mA). Participants used the LF-EMS or sham for 1 h, five times a week, for 8 weeks. Four of the five sessions were at home and one under supervision.

### Measurements

Brachial artery endothelium-dependent vasodilation was assessed using the flow-mediated dilation (FMD) technique following recommended methods.<sup>9</sup> Briefly, the brachial artery was imaged using high-resolution ultrasound (Tersaon t3000, Aloka, UK) to detect the change in arterial diameter in response to a 5 min ischaemic stimulus induced by forearm cuff inflation to 220 mmHg.<sup>9</sup> Diameter, flow, and shear stress were measured prior to and following 5 min of forearm cuff inflation. Analysis was performed using custom-designed edge-detection and wall-tracking software by a single person who was blinded to treatment allocation. Allometric scaling for baseline diameter was performed.<sup>10</sup> Maximal cardiopulmonary exercise testing was performed in accordance with American Thoracic Society guidelines<sup>11</sup> on an upright cycle ergometer with an exercise respiratory gas analysis system (Oxycon Pro, Jaeger, Warwick, Warwickshire, UK). All assessments were performed prior to and following LF-EMS or sham.

**Table 1** Baseline demographic and clinical characteristics of the LF-EMS and sham placebo groups

	EMS intervention ( $n = 20$ )	Sham ( $n = 15$ )	<i>P</i> value
<b>Demographics</b>			
<i>N</i> , Male	13 (65%)	10 (66.6%)	0.92
Age (years)	68.6 $\pm$ 9.4	66.7 $\pm$ 6.8	0.59
BMI (kg/m <sup>2</sup> )	29.5 $\pm$ 4.7	27.8 $\pm$ 5.4	0.1
<b>Clinical</b>			
NT-proBNP (pg/mL)	3052 $\pm$ 3398	2132 $\pm$ 2012	0.23
Creatinine ( $\mu$ mol/L)	101 $\pm$ 47	109 $\pm$ 41	0.45
LVEF %	39 $\pm$ 11	22 $\pm$ 12	0.42
BP <sub>sys</sub> (mmHg)	116 $\pm$ 19	123 $\pm$ 14	0.16
BP <sub>dia</sub> (mmHg)	67 $\pm$ 11	70 $\pm$ 8	0.23
NYHA III	14 (70%)	11 (73.3%)	0.83
NYHA IV	6 (30%)	4 (26.7%)	0.83
<b>Co-morbidities</b>			
Prev MI/PCI/CABG	13 (65%)	8 (53.3%)	0.49
Diabetes	10 (50%)	7 (46.6%)	0.84
COPD	5 (25%)	3 (20%)	0.73
AF	14 (68%)	9 (60%)	0.62
Hypertension	9 (45%)	7 (46.6%)	0.92
CKD	5 (25%)	9 (60%)	0.03

AF, atrial fibrillation; BMI, body mass index; BP<sub>dia</sub>, diastolic blood pressure; BP<sub>sys</sub>, systolic blood pressure; CABG, coronary artery bypass graft surgery; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LF-EMS, low-frequency electrical muscle stimulation; LVEF, left ventricular ejection fraction; NT-proBNP, N terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Data presented as mean  $\pm$  standard deviation or absolute number and per cent.

### Statistical analysis

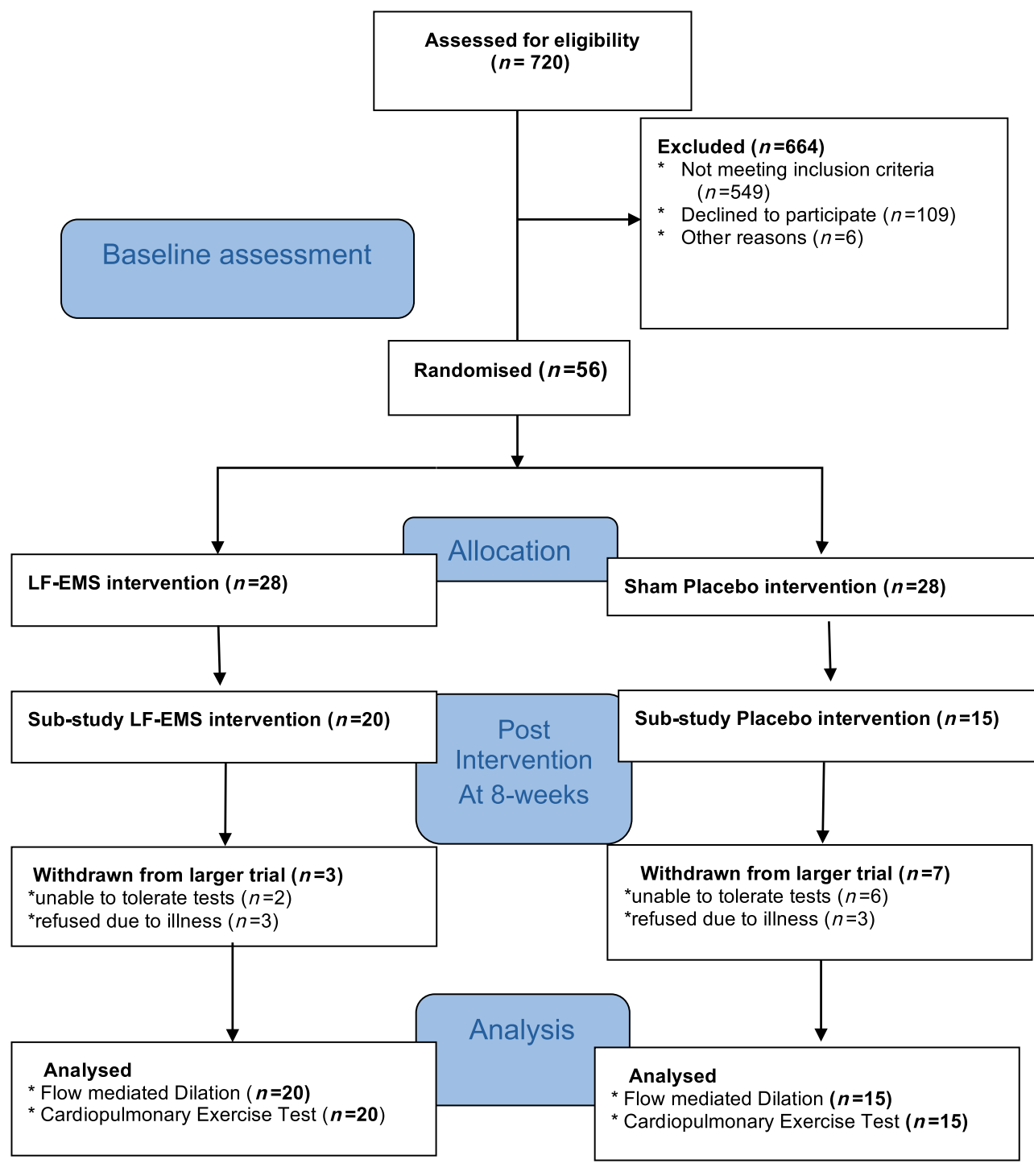
Given that this is a feasibility study, no a priori sample size was calculated. The sample size of each group in this current sub-study provides 47% power to detect a between-group difference in FMD of 1.0% (equivalent to a 20% decreased mortality in patients with CHF<sup>3</sup>) assuming a standard deviation of 1.5% for within group change scores and using a two-sided independent *t*-test (G\*Power 3.1.5).<sup>12</sup> This sample size was deemed appropriate to enable an estimate of sample size for a larger trial.

Delta changes ( $\Delta$ ) from pre-intervention were calculated for each group and entered as the dependent variable in a linear mixed model (Statistical Package for the Social Sciences, Version 20: SPSS Inc., Chicago, IL) with pre-intervention data entered as a covariate. Data are presented in the text as mean and 95% confidence intervals with exact *P* values.

### Results

Brachial artery FMD improved by 2.56% (95% confidence interval: 0.69 to 3.80) with LF-EMS compared with sham (*Figure 2*), which approached statistical significance

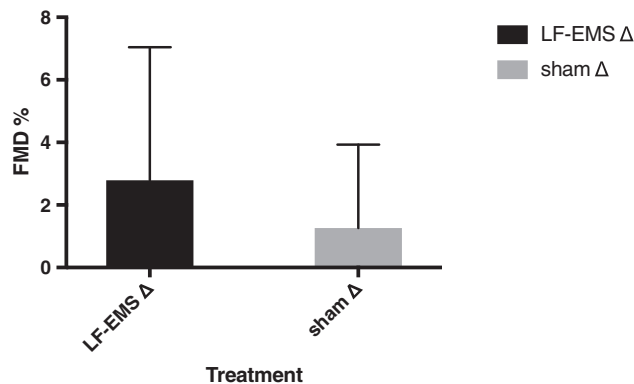
**Figure 1** Consort diagram of the study; low-frequency electrical muscle stimulation (LF-EMS) vs. sham placebo in severe heart failure patients.



( $P = 0.07$ ). Based on this outcome, it was estimated that 86 participants per group would be required to have 80% power to detect a statistically significant ( $P < 0.05$ ) between-group differences in FMD.

There was also a trend towards a smaller arterial diameter (Table 2) with sham vs. LF-EMS ( $P = 0.08$ ). There were no notable intervention-mediated changes in peak arterial diameter or shear rate and time to peak. There were negligible

**Figure 2** Mean flow-mediated dilation (FMD) change after 8-week low-frequency electrical muscle stimulation (LF-EMS) or sham. Error bars are standard deviations.



changes in  $VO_{2peak}$  in both groups following the 8 week intervention period (Table 2).

## Discussion

We provide preliminary evidence towards enhanced endothelial function following LF-EMS compared with sham in patients with CHF NYHA III/IV. Despite no notable changes in  $VO_{2peak}$ , these data suggest that the impact of LF-EMS on endothelial function should be explored in a larger trial.

This is the first study to assess the impact of LF-EMS on FMD in patients with advanced CHF. Our data suggest that a sample size of 86 patients per group would be required to show statistical improvement in FMD with LF-EMS. We show preliminary evidence of a clinically relevant improvement in FMD greater than 1%.<sup>3</sup> An improvement of similar or greater magnitude in FMD with a fully powered, larger study would be important for this group of high-risk patients, given that (i) a 1% increase in FMD is associated with a 20% decreased mortality in CHF patients<sup>3,7</sup> and (ii) this group of patients are physically debilitated and generally contradicted for exercise-based cardiac rehabilitation. Therefore, LF-EMS may offer an alternative means to conventional exercise in altering blood flow (shear) stress patterns against the artery walls to improve vascular function. A noteworthy observation to support the endothelial function data was evidence of a decrease in artery size in the sham intervention. A change in artery size may suggest that the health of the artery is deteriorating possibly related to persistent physical inactivity,<sup>13</sup> but a positive impact of LF-EMS on artery size may maintain or augment endothelial function.

The measurement of  $VO_{2peak}$  is challenging in this population. Many participants were unable to meet the

**Table 2** Changes in endothelial function and CPET performance after 8-week EMS or sham intervention

	Pre-LF-EMS	LF-EMS Δ change	Pre-sham	Sham Δ change	P
<b>Endothelial function</b>					
FMD (%)	5.48 (4.34 to 6.32)	2.79 (0.8 to 1.99)	5.43 (3.47 to 7.39)	1.26 (-0.22 to 2.7)	0.075
Baseline diameter(cm)	0.43 (0.39 to 0.47)	0.00(-0.02 to 0.01)	0.46 (0.42 to 0.5)	-0.01 (-0.04 to 0.02)	0.086
Peak diameter (cm)	0.46 (0.42 to 0.49)	0.01 (-0.01 to 0.03)	0.48 (0.45 to 0.52)	0.00 (-0.03 to 0.03)	0.268
Shear rate <sub>AUC</sub>	14 048.71 (10 127.90 to 17 969.52)	-2735.94 (-7148.93 to 1677.07)	12 700.18 (7269.49 to 18 130.87)	1127.39 (-5262.84 to 7517.63)	0.953
Time to peak (s)	73.45 (57.52 to 89.37)	-11.00 (-31.83 to 9.82)	70.04 (48.94 to 91.13)	4.09 (-28.16 to 36.34)	0.887
Maximal O <sub>2</sub> uptake	13.87 (12.47 to 15.26)	-0.19 (-1.05 to 0.69)	12.87 (10.99 to 14.75)	0.06 (-0.75 to 0.87)	0.922
VO <sub>2</sub> peak (mL/kg/min)	67.25 (56.12 to 78.38)	-1.70 (-9.01 to 5.61)	69.12 (53.94 to 84.29)	-2.29 (-7.64 to 3.05)	0.999
Max watts output	8.84 (7.31 to 10.38)	-0.11 (-0.2 to 2.3)	8.05 (6.21 to 9.89)	0.64 (0.18 to 0.32)	0.893
Anaerobic threshold (mL/kg/min)					

CPET, cardiopulmonary exercise testing; FMD, flow-mediated dilation; LF-EMS, low-frequency electrical muscle stimulation. Data was analysed using general estimating equations and presented as mean (95% CI). Delta (Δ) change from baseline values (95%CI).

requirements for peak oxygen uptake including respiratory exchange ratio < 1.10 and test duration < 8 min,<sup>13</sup> suggesting musculoskeletal issues rather than oxygen uptake were limiting exercise capacity. Given these issues, together with the findings from the 6 min walk test previously reported, measuring  $VO_{2peak}$  in any larger study may not be appropriate.

Participants were deemed eligible for the study based on the judgement of experienced heart failure clinicians using available knowledge. This may have led to greater variability in disease severity/limitation between groups; this potential confounding can be factored into the randomization procedure of any large trial.

In summary, LF-EMS could be useful in improving FMD in patients with CHF NYHA III/IV, which could improve mortality and should be explored in a larger trial.

## Conflict of interest

None declared.

## Author contributions

S.E., G.M., and P.B. conceived the work; S.E., G.M., P.B., B.M., H.J., and R.S. designed the work; S.E. and G.M. acquired the data; S.E., G.M., P.B., B.M., H.J., R.J., and A.T. analysed and interpreted the data; S.E. and H.J. drafted the manuscript; P.B., B.M., H.J., R.S., and A.T. revised the manuscript; All gave final approval and agree to be accountable for integrity and accuracy of this work.

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