



University of Dundee

## Transcutaneous Electrical Nerve Stimulation improves walking performance in patients with intermittent claudication

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# The Journal of Cardiovascular Nursing

## Transcutaneous Electrical Nerve Stimulation (TENS) improves walking performance in patients with Intermittent Claudication (IC)

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<b>Abstract:</b>	<p>The purpose of this study was to investigate the effects of two types of Transcutaneous Electrical Nerve Stimulation (TENS) on walking distance and measures of pain in patients with Peripheral Arterial Disease (PAD) and Intermittent Claudication (IC). In a phase 2a study, forty participants with PAD and IC completed a graded treadmill test on two separate testing occasions. Active TENS was applied to the lower limb on the first occasion and placebo TENS on the second. Participants were divided into two experimental groups. One group received High-Frequency TENS (HF-TENS), the other Low-Frequency TENS (LF-TENS). Measures taken were: Initial Claudication Distance (ICD), Functional Claudication Distance (FCD) and Absolute Claudication Distance (ACD). The McGill Pain Questionnaire (MPQ) vocabulary was completed at the end of the intervention and the MPQ-Pain Rating Index (PRI) score calculated. Four participants were excluded from the final analysis due to non-completion of the experimental procedure. Median walking distance increased with HF-TENS for all measures (<math>p &lt; .05</math>, Wilcoxon signed ranks test, all measures). Only ACD increased significantly with LF-TENS compared to placebo (Mdn = 179 to 228, <math>W_s = 39</math>, <math>z = 2.025</math>, <math>p = 0.043</math>, <math>r = 0.48</math>). No difference was observed between reported median MPQ-PRI scores: 21.5 with placebo TENS and 21.5 with active TENS (<math>p = .41</math>). TENS applied to the lower limb of patients with PAD and IC was associated with increased walking distance on a treadmill but not with any reduction in pain. TENS may be a useful adjunctive intervention to help increase walking performance in patients with IC.</p>

## Abstract

The purpose of this study was to investigate the effects of two types of Transcutaneous Electrical Nerve Stimulation (TENS) on walking distance and measures of pain in patients with Peripheral Arterial Disease (PAD) and Intermittent Claudication (IC). In a phase 2a study, forty participants with PAD and IC completed a graded treadmill test on two separate testing occasions. Active TENS was applied to the lower limb on the first occasion and placebo TENS on the second. Participants were divided into two experimental groups. One group received High-Frequency TENS (HF-TENS), the other Low-Frequency TENS (LF-TENS). Measures taken were: Initial Claudication Distance (ICD), Functional Claudication Distance (FCD) and Absolute Claudication Distance (ACD). The McGill Pain Questionnaire (MPQ) vocabulary was completed at the end of the intervention and the MPQ-Pain Rating Index (PRI) score calculated. Four participants were excluded from the final analysis due to non-completion of the experimental procedure. Median walking distance increased with HF-TENS for all measures ( $p < .05$ , Wilcoxon signed ranks test, all measures). Only ACD increased significantly with LF-TENS compared to placebo ( $Mdn = 179$  to  $228$ ,  $W_s = 39$ ,  $z = 2.025$ ,  $p = 0.043$ ,  $r = 0.48$ ). No difference was observed between reported median MPQ-PRI scores: 21.5 with placebo TENS and 21.5 with active TENS ( $p = .41$ ). TENS applied to the lower limb of patients with PAD and IC was associated with increased walking distance on a treadmill but not with any reduction in pain. TENS may be a useful adjunctive intervention to help increase walking performance in patients with IC.

## Keywords

Peripheral arterial disease, intermittent claudication, transcutaneous electrical nerve stimulation (TENS), ischaemic pain, exercise therapy

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## TEXT

### **Introduction:**

Peripheral Arterial Disease (PAD) is a clinical manifestation of atherosclerosis. Intermittent claudication (IC) is the most common manifestation, and is reported to affect between 10 and 30% of the population aged above 60 years of age.<sup>1</sup> PAD can be asymptomatic in the early stages, however as the disease progresses, the increasing atherosclerosis manifests as IC,<sup>2</sup> which is the cardinal symptom of PAD. IC is defined as pain in the lower limb(s) that is experienced during walking, and is relieved by rest.<sup>3,4</sup> Patients experiencing IC are characterised by reduced levels of daily physical activity, which is associated with diminished performance of personal, social and occupational activities of daily life. Many individuals become housebound or dependent on others<sup>5,6</sup> and studies suggest that patients with severe IC have a quality of life that equates to those with terminal cancer.<sup>7</sup>

The management of PAD and IC is primarily through the modification of risk factors, with endovascular intervention in severe cases and most medical therapies having only a modest benefit.<sup>8,9</sup> Exercise therapy, particularly supervised, is a mainstay of PAD and IC management that has been shown to have a significant effect on increasing walking distance, self-reported physical activity, measured cardio-respiratory fitness, exercise time and functional ability.<sup>3,10-16</sup> Despite the clear benefits of exercise therapy, over 45% of patients are non-compliant with healthcare professional advice to take regular exercise and to walk 'through' IC pain.<sup>11</sup> The pain associated with IC has been identified as a key barrier to walking.<sup>17</sup> Although acknowledged as a problem, there is little published literature examining analgesic interventions for IC pain.

Transcutaneous Electrical Nerve Stimulation (TENS) is a safe, inexpensive and non-invasive method of providing mild electrical stimulation for the relief of pain.<sup>18,19</sup> TENS has been reported to provide greater analgesic effects than placebo TENS for musculoskeletal,<sup>20</sup> postoperative<sup>21</sup> and neuropathic pain.<sup>22</sup> Packaged in a compact, portable unit that is easy to apply via small electrodes placed on the skin, a TENS unit can be kept unobtrusively in a pocket, or clipped to a trouser belt whilst being used to reduce pain and improve daily functioning.<sup>23</sup>

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4 However, thus far TENS has not been tested as a method of reducing pain and improving  
5 walking related function in patients with IC pain.  
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10 There are two main stimulation patterns, or dosages, of TENS employed in clinical practice:  
11 High-Frequency TENS (HF-TENS) and Low Frequency TENS (LF-TENS). Studies conducted to date  
12 suggest that the fast-acting, reflexive mechanism of HF-TENS may act most effectively at the  
13 mild (pain threshold) level of the pain experience. LF-TENS however may act most effectively at  
14 the stronger (pain tolerance) level of the pain experience due to extrasegmental but longer-  
15 lasting analgesic effects.<sup>23</sup>  
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23 In addition, although TENS has not been widely tested as a method of pain relief of IC, a  
24 previous investigation observed reductions in pain (hypoalgesia) with High Frequency TENS (HF-  
25 TENS) in healthy volunteers experiencing experimentally-induced ischaemic pain in the lower  
26 limb.<sup>24</sup> This may be due to the focus on exercise, and endovascular intervention as treatments  
27 for the condition and limited investigation into the nature of IC pain. Also the potential for high  
28 frequency verses low frequency patterns of TENS to affect different portions of the IC pain  
29 experience has not been examined.  
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39 We hypothesised that the two types of TENS might favourably, but differentially, affect discrete  
40 portions of the IC pain experience; for instance, when pain is mild (which normally occurs in  
41 PAD patients after walking a short distance), or when it becomes more severe (during  
42 continued walking). We therefore aimed to investigate the effects of HF and LF-TENS on  
43 measures of pain and walking performance in patients with PAD and IC.  
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4 **Material and Methods:**  
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6 *Participants:*  
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8 Ethical approval for the study was obtained from the NHS East of Scotland Research Ethics  
9 Service (Reference Number: 09/S1402/15). Forty participants with stable PAD and IC were  
10 recruited from the vascular outpatient clinic at Ninewells Hospital, Dundee, Scotland and block  
11 randomised into two experimental groups (HF-TENS and LF-TENS). Participants provided  
12 written informed consent and were included if they had: clinical diagnosis of PAD and stable IC  
13 of more than 3 months duration; Fontaine stage II claudication; resting Ankle Brachial Index  
14 (ABI) less than 0.90 in at least one leg; walking limited only by claudication; independent and  
15 safe mobility (no walking aids); were cognitively stable and able to follow instruction and were  
16 able to read and complete the questionnaires. Participants were excluded if they were: less  
17 than 40 years of age; had planned surgical or endovascular intervention for PAD; co-morbidities  
18 causing pain in the lower limb; ataxic gait or history of increased falls (unsafe for treadmill  
19 walking); myocardial infarction within the previous 6 months, cardiac arrhythmia or a cardiac  
20 pacemaker; current or previous sensation abnormalities in the lower limbs; epilepsy; medical  
21 diagnosis or self-reported psychiatric illness or previous experience of using TENS.  
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37 *Study Protocol:*  
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39 The experimental study design was a single blind, placebo-controlled, phase 2a, proof-of-  
40 concept trial. Each participant attended for two sessions, six to nine days apart with the  
41 majority of participants (n=30) completing both tests within seven days. A graded treadmill  
42 protocol<sup>25</sup> was completed by the participant at each. On the first occasion active TENS was  
43 applied and placebo TENS (P-TENS) on the second. For the purpose of blinding, the participants  
44 were told that “different ‘dosages’ of TENS were being tested, some of which may not be  
45 perceptible”. To enhance blinding and reduce the risk of bias, one researcher applied the TENS  
46 and a different researcher, who was blinded to the study protocol and the order of  
47 intervention, conducted the treadmill test and recorded the primary outcome measures.  
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58 *Treadmill Procedure:*  
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4 The treadmill procedure followed that described by Gardner et al <sup>25</sup> using a GE Marquette  
5 treadmill. Participants were connected to a 12-lead Echocardiograph (12-lead ECG) (GE CASE  
6 Premium Stress System), which recorded continuously throughout the procedure. A  
7  
8 familiarisation session was completed first where participants practiced walking at different  
9 speeds (1, 1.5 and 2mph) and the self-report method of rating claudication symptoms was  
10 explained. Further safety instructions were also issued: the participants were reminded to  
11 report any feelings of pain distinct from claudication and any feelings of dizziness/light-  
12 headedness immediately so that the test could be stopped. This series of events took less than  
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14 10 minutes to complete and the participant walked for a maximum of 30 seconds at each  
15 treadmill speed. Once this familiarisation procedure was completed, participants rested supine  
16 on a bed for 15 minutes in preparation for the full treadmill test.  
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27 *TENS Procedure:*

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29 A NeuroTrac 3™ TENS machine (Verity Medical Ltd, Surrey, UK) was fitted to the participant five  
30 minutes prior to each treadmill test and continued throughout the procedure. A segmental  
31 electrode application was employed using self-adhesive carbon rubber electrodes measuring  
32 5x5 cm (PhysioMed PALS® electrodes, Glossop, UK). The two electrodes were attached to the  
33 TENS unit via the manufacturer leads. The area of pain reported by the participant during the  
34 familiarisation session determined the electrode placement sites. The placement sites were at  
35 least 2cm apart. Electrodes were commonly placed with one proximal and one distal to the  
36 gastrocnemius muscle belly.  
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47 The TENS machine was calibrated prior to use with a digital oscilloscope and tested manually by  
48 the investigator prior to every testing session. The HF-TENS stimulation parameters were  
49 calibrated to 120Hz, pulse width 200µs and patient determined intensity of “strong but  
50 comfortable”. The LF-TENS stimulation was set at 2Hz, pulse width 200µs and patient  
51 determined intensity of “strong but comfortable and slight muscle twitch”.  
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4 The placebo TENS (P-TENS) condition used the same TENS model and programmed settings but  
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6 with an inconspicuous break in the wires. This allowed the unit to be switched on with the  
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8 appearance of a working unit but without any current reaching the participant. This was  
9  
10 checked and confirmed with the use of an oscilloscope as described above.  
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#### 14 *Measures:*

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16 Participants were instructed to report:

- 17 1. When they first experienced claudication symptoms (Initial Claudication Distance (ICD))  
18 <sup>25</sup>
- 19 2. When they reached the point at which they would usually stop walking (Functional  
20 Claudication Distance (FCD)) <sup>26,27</sup>
- 21 3. When they could not walk any further due to claudication symptoms (Absolute  
22 Claudication Distance (ACD)) <sup>25</sup>

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31 Pain quality and intensity was recorded using a McGill Pain Questionnaire (MPQ); <sup>28</sup>  
32 administered 5 minutes after the participant completed the treadmill protocol. The MPQ  
33 consists of a vocabulary of adjectives from which the participant chooses appropriate words to  
34 describe the particular qualities of IC pain and accompanying feelings of distress and  
35 intrusion.<sup>29</sup>  
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#### 43 *Statistical Analysis:*

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45 The mean scores for ICD, FCD and ACD were positively skewed and showed heteroscedascity. A  
46 log (10) transformation applied to normalise the data did not address the variance within the  
47 data, thus non-parametric statistics were used to analyse the data.  
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53 Wilcoxon Signed Ranks tests examined within-group differences in treadmill measures and  
54 MPQ-PRI scores. In order to reduce the effect of inter-participant variability, individual change  
55 in ICD, FCD and ACD between P-TENS and Active TENS was calculated for each participant.  
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58 Distance walked with P-TENS was subtracted from the distance walked with Active TENS. <sup>30</sup>  
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Individual percentage change was also calculated for ICD, FCD and ACD. The difference between the two sessions was calculated as a percentage of the distance walked with P-TENS. These values were then analysed using Mann-Whitney U tests for between-group comparisons. Statistical significance was set at  $p = 0.05$  (two-tailed) and analysis was performed using SPSS version 19.0.

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4 **Results:**

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6 *Participants:*

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8 Four participants were excluded from analysis due to non-completion of the experimental  
9 procedure. Three had previously unknown exercise-limiting co-morbidities and one was unable  
10 to walk safely on the treadmill. The remaining 36 participants (18 in each group) were included  
11 in the analysis (29 male, mean age (range) = 70 (54-87) years). Figure 1 summarises this  
12 information and displays the flow of participants through the study. The groups were similar in  
13 terms of demographic and disease data. The LF-TENS group had a significantly lower mean ABI  
14 (0.57 vs 0.63,  $t(34) = 2.442$ ) (Table 1).  
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24 *Within Group Profiles (HF-TENS and LF-TENS vs. P-TENS):*

25 ICD, FCD and ACD results are detailed in Table 2. Compared to placebo TENS, median walking  
26 distance increased with TENS intervention in both groups. This was true with the exception of  
27 FCD in the HF-TENS group (Mdn 187 to 175m) and ICD in the LF-TENS group (Mdn 81 to 76m).  
28 All walking-related outcome measures changed with HF-TENS intervention. Only ACD changed  
29 with LF-TENS intervention (Mdn 179 to 288m,  $W_s = 39$ ,  $z = 2.025$ ,  $p = 0.043$ ,  $r = 0.48$ ). There was  
30 no change in MPQ-PRI scores for either group (Table 2).  
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40 *Between Group Profiles (HF-TENS vs. LF-TENS):*

41 There was an overall increase in all measures in both groups as shown by the positive change  
42 values in Figures 2 and 3. The only difference between the groups was in change and  
43 percentage change in ICD (Mdn (IQR) = 26 (71) with HF-TENS and 6 (67) with LF-TENS,  $U = 268$ ,  $z$   
44 = 2.073,  $p = 0.038$ ,  $r = 0.49$  and Mdn (IQR) = 43 (64) with HF-TENS and 9 (79) with LF-TENS,  $U =$   
45 267,  $z = 2.088$ ,  $p = 0.037$ ,  $r = 0.49$  respectively) (Figures 2 and 3).  
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4 **Discussion:**  
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6 The results of this study indicate that compared to placebo, the application of TENS whilst  
7 walking on a treadmill is associated with a modest but statistically significant improvement of  
8 walking performance in patients with IC. These results indicate that TENS offers potential as a  
9 clinically useful intervention that allows patients with IC to walk further before onset of pain,  
10 and while experiencing pain.  
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18 The two different stimulus patterns of TENS employed in this study were found to affect  
19 distinctive aspects of the pain experience. ICD and ACD increased with HF-TENS whereas only  
20 ACD increased with LF-TENS. The different stimulus patterns of HF-TENS and LF-TENS appear to  
21 have activated different mechanisms of hypoalgesia and distinct neurophysiological effects.  
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27 Increases in ICD and ACD were observed in the HF-TENS group suggesting an immediate and  
28 prolonged hypoalgesic effect. Median FCD decreased with HF-TENS intervention however, this  
29 appeared to be due to the large variance within the sample, as illustrated by an increase in IQR  
30 (Table 2). Also, when correcting for baseline ability (change scores, Figure 2), median FCD was  
31 found to be greater than zero therefore indicating an overall increase in walking distance. The  
32 increases in median ICD and ACD with HF-TENS were found to be significant with effect sizes of  
33 .69 ( $p = .004$ ) and .53 ( $p = .025$ ) respectively (Table 2 and Figures 2 and 3). In the LF-TENS group,  
34 there was a decrease in median ICD but increases in FCD and ACD suggesting a delayed but  
35 effective hypoalgesic effect at pain tolerance. The increase in ACD with LF-TENS was found to  
36 be significant with an effect size of .48 ( $p = .043$ ) (Table 2). These findings suggest that HF-TENS  
37 had an immediate and lasting effect; increasing walking distance at the mild (ICD) and more  
38 severe phases of the pain experience (ACD). The effects of LF-TENS however, were only evident  
39 when the pain was severe (ACD) indicating a delayed action. These results must be interpreted  
40 with caution as the significantly lower ABI in the LF-TENS group indicates more severe PAD  
41 which could have contributed to the poor response. A further variable is the sequencing of the  
42 placebo after the TENS treatment which could have un-blinded the study for the participants  
43 and led to less of a response when no stimulation was perceived.  
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6 HF-TENS is proposed to act by activating large diameter mechanoreceptors ( $A\beta$ -fibres), delta  
7 ( $\delta$ )-opioid receptors and increasing gamma-Aminobutyric acid (GABA) in the spinal cord. It is  
8 associated with immediate, localised, segmental inhibition as conceived by the original gate  
9 control theory.<sup>31,32</sup> LF-TENS was originally theorised to act on smaller diameter nociceptive  
10 afferents, brainstem structures and supraspinal descending pathways, releasing endogenous  
11 opiates centrally and peripherally.<sup>32,33</sup> In contrast to HF-TENS, it was thought that LF-TENS did  
12 not induce immediate hypoalgesia but had a latent effect of pain relief due to its more complex  
13 mechanisms.<sup>34</sup> These differential mechanisms of action have recently been challenged.<sup>35</sup>  
14 Nevertheless, the originally proposed mechanisms of action would explain the characteristics of  
15 hypoalgesia evident in the current study.  
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27 Our 'proof of concept' results indicate that HF-TENS improved walking performance during the  
28 period of treadmill walking that would normally correspond with the first appearance of IC pain  
29 and when it is growing in intensity. In contrast, LF-TENS did not appear to affect walking  
30 performance in those portions of the walking exercise. Instead, the effect of LF-TENS  
31 corresponds with that later period of treadmill walking when IC pain would normally be most  
32 severe and intolerable.  
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41 There is no consensus in the literature regarding modification of which aspect of the IC pain  
42 experience (ICD, FCD or ACD) results in the greatest gains in walking performance and therefore  
43 the most effective management. From the results of the current study it would seem that HF-  
44 TENS might be more effective due to the hypoalgesic effects evident throughout the pain  
45 experience. These conclusions however are tentative and future investigations could further  
46 explore the relationships between the IC pain experience and different applications of TENS.  
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54 Pain relief is thought to be the primary action of TENS however, neither TENS group reported  
55 any change in MPQ-PRI scores. Whereas the results suggest that pain intensity was not  
56 affected, an alternative explanation could be related to the experimental methodology. The  
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4 MPQ was completed at the end of the treadmill test and participants were asked to describe  
5 their pain at ACD. The participants were therefore walking to the same level of pain intensity on  
6 both occasions. As discussed above, ACD increased with both types of TENS intervention and  
7 thus, even though there was no change in maximum pain intensity, the distance walked before  
8 ACD was reached was greater when using TENS compared to placebo. This result indicates that  
9 TENS, rather than masking and reducing the experience of maximum pain in patients walking  
10 with IC pain, prolongs the time taken to reach pain tolerance. This finding is in line with results  
11 of our experimental study of TENS for laboratory-induced lower limb ischaemic pain in healthy  
12 volunteers.<sup>24,36</sup>  
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23 Compared to P-TENS, the median change in ACD with HF-TENS was 30 metres (m) and with LF-  
24 TENS, 23m. This relates to percentage increases of 13% for HF-TENS and 18% with LF-TENS  
25 (Table 3 and Figure 3). A 60% improvement in ACD has been suggested as a functionally  
26 significant improvement in walking distance for patients with IC.<sup>37</sup> The observed effect of TENS  
27 on walking performance in the current study, conducted within the operational constraints  
28 imposed by a routine PAD clinic setting, was such that one might anticipate a degree of  
29 'dampening' of the potential effect of TENS. A familiarisation or training effect has been shown  
30 with the Gardner treadmill test.<sup>38</sup> Cognisant of this fact, P-TENS condition was examined on the  
31 second testing session for every participant. By the nature of this design, any effect of TENS  
32 observed would be masked by the potential accommodation effect during the second treadmill  
33 test. The training/accommodation effect for the Gardner treadmill protocol has been found to  
34 be 15% for ACD.<sup>38</sup> With this in mind, the significant increases of 13% and 18% with HF and LF-  
35 TENS may become closer to a clinically worthwhile improvement. IC medication is associated  
36 with an increase of approximately 30% compared to placebo.<sup>39</sup> The change in ACD with TENS  
37 intervention, taking into account the possible treadmill walking accommodation effect (10%) is  
38 close to this level of improvement (increase of 23% and 28% compared to placebo). **Future  
39 studies should include treadmill familiarisation and employ a randomised order of entry,  
40 crossover design to more accurately explore the effect of TENS on walking performance in  
41 patients with IC.**  
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6 This study makes a novel contribution to the literature on the management of PAD and IC.  
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8 There is no previously published report of the effect of TENS on walking performance and pain  
9  
10 in this patient population. Our clinical results are also supported by our previous publication on  
11  
12 HF-TENS for ischaemic pain in healthy volunteers.<sup>24</sup> However this is a ‘proof of concept’ study.  
13  
14 Further study could examine the effectiveness of TENS as an adjunctive intervention for walking  
15  
16 performance in patients with IC in more detail. For example, further investigation is required  
17  
18 that examines the effects on pain, haemodynamic changes and gait during treadmill walking.  
19  
20 There is also a need for investigations that explore the effects of TENS on IC-limited walking in  
21  
22 people with PAD during more ecologically valid (over ground) walking tasks.  
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26 *Limitations:*

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28 One aspect of the current study that could be viewed as a limitation is the lack of a no-TENS  
29  
30 control group. By neglecting to include a no-TENS control condition it was not possible to  
31  
32 accurately quantify the effect of the placebo effect of TENS. It has been proposed that part of  
33  
34 the beneficial effect of TENS is the sense of ‘control’ and the perception of receiving an  
35  
36 ‘intervention’ experienced by patients when applying the device. Without a no-TENS group this  
37  
38 effect cannot be quantified. The study was designed as a proof-of-concept, MRC Phase 2a trial  
39  
40 and a pragmatic approach was assumed. When investigating the effects of TENS with the aim of  
41  
42 evaluating physiologically quantifiable outcomes, TENS must demonstrate efficacy above  
43  
44 placebo therefore the current study design is sufficient. Nevertheless, future studies should  
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46 include a no-TENS control to allow investigation of the placebo response to TENS in PAD and IC.  
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50 Another possible limitation of this study was the ordering of intervention. As the treadmill test  
51  
52 with active TENS preceded the application of placebo for all participants, any effect of TENS  
53  
54 observed could be temporal. This design was selected to account for participant familiarisation  
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56 with the treadmill test. Previous research has indicated that participants commonly walk  
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58 approximately 15% further during subsequent graded treadmill tests<sup>37</sup>. What this design  
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60 achieves is that any signal detected (i.e. an increase in walking distance with TENS) must have  
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4 first exceeded the 'noise' of familiarisation. Overall, this design 'handicapped' the study and  
5  
6 ensured that any findings are more cautious.  
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10 *Conclusions:*

11 Patients with IC experience a gradual build-up of pain to tolerance when exercising until the  
12 pain becomes intolerable. The current study aimed to investigate the effects of two types of  
13 TENS (high and low frequency) on the pain experienced and walking performance in patients  
14 with PAD and IC. The results indicate that TENS increases the distance walked before tolerance.  
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16 Both types of TENS were found to increase walking performance but HF-TENS was more  
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18 effective at prolonging the time to reach pain threshold.  
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Table 1: Demographic and baseline data for all participants. *p* values relate to independent student's t-tests (two tailed) of the group values

Table 2: Median (IQR) ICD, FCD and ACD (in metres) and MPQ-PRI scores for both groups with placebo and with TENS intervention

Figure 1: CONSORT diagram displaying the progression of participants through the study.

Figure 2: Boxplots representing change in walking measures (metres) with TENS intervention in both groups. Positive values represent a positive change with TENS intervention over placebo.

Figure 3: Boxplots representing percentage change in walking measures with TENS intervention in both groups. Positive values represent a positive change with TENS intervention over placebo.



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8<sup>th</sup> January 2015

Dear Editor,

You had requested clarification regarding a number of points. Please find below an explanation of how these issues have been addressed in the revised manuscript.

1. P2, L55: the sentence beginning with "packaged in a compact ... " is incomplete
  - *Manuscript edited to include: "Packaged in a compact, portable unit that is easy to apply via small electrodes placed on the skin, a TENS unit can be kept unobtrusively in a pocket, or clipped to a trouser belt whilst being used to reduce pain and improve daily functioning."*
2. P4: Was a power calculation completed to determine sample size?
  - *As the study was designed as a 'proof of concept' trial, a sample size of 40 participants was selected as feasible prior to a power calculation. A post-hoc power calculation was performed and found that using 80% power and a two-tailed 5% significance level this sample would be able to detect a large effect ( $\geq 0.8$ ; (Cohen 1988)) between two groups.*
3. How was group assignment determined?
  - *Participants were 'block randomised' into the two groups, detailed in the manuscript on Page 4, Line 12-14*
4. It's unclear where the placebo walk came in. Why was the TENS walk completed first and then the placebo walk. Wouldn't it have been cleaner to randomize the order?
  - *The ordering of interventions was an aspect that stimulated much discussion within the team. The consensus from previous experience, in addition to review of the literature, was that participants often demonstrated a treadmill familiarisation effect i.e. walked further during subsequent treadmill tests to a degree of approximately 10-15% (Labs et al 1999, Vascular Medicine, 4; pp 239-246). With this in mind, it was decided that the most conservative approach should be taken with participants experiencing the active TENS condition first.*
  - *What this design achieves is that any signal detected (i.e. an increase in walking distance with TENS) must have first exceeded the noise of familiarisation. Overall, this design 'handicapped' the study and made sure that any conclusions arrived at were more cautious. In addition, participants undertook treadmill familiarisation in accordance with the Gardner treadmill protocol (Gardner et al 1991, Medicine and*

1  
2 *Science in Sports and Exercise, 23 pp 402-408). These sessions of treadmill walking*  
3 *would have helped to reduce any training effect.*

- 4 • *Nevertheless, we appreciate the point raised and the 'Limitations' includes this*  
5 *discussion point and the Discussion reflects that the application of TENS is merely*  
6 *"associated" with modest increase in walking performance rather than "elicits".*  
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- 9
- 10 5. Even though the treadmill tester was blinded, didn't they know that the first test was  
11 the TENS test and the second test placebo?
- 12
  - 13 • *No, the treadmill tester was not aware of the study protocol or the order in which the*  
14 *interventions were applied.*
  - 15
  - 16 • *Manuscript edited to include: "To enhance blinding and reduce the risk of bias, one*  
17 *researcher applied the TENS and a different researcher, who was blinded to the study*  
18 *protocol and the order of intervention, conducted the treadmill test and recorded the*  
19 *primary outcome measures. "*  
20
- 21
- 22 6. P5, L47-55: Were patients able to discern the differences between "strong but  
23 comfortable" and "strong but comfortable and slight muscle twitch"?
- 24
  - 25
  - 26 • *Participants were aided in this by the researcher who applied all dosing of TENS. For the*  
27 *greater intensity required with LF-TENS the researcher ensure slight but visible muscle*  
28 *twitch before beginning the treadmill protocol.*  
29
- 30
- 31 7. p6: please provide a reference for the adjustment for the P-TENS walk (L59)
- 32
  - 33
  - 34 • *Manuscript edited to include reference to Vickers and Altman 2001, BMJ, 323: 7321, pp*  
35 *1123-1124 (Page 6, Line 59)*  
36
- 37
- 38 8. P8: please list in the narrative, how many patients were assigned to each group
- 39
  - 40
  - 41 • *Manuscript edited to include: "The remaining 36 participants (18 in each group) were*  
42 *included in the analysis"*
  - 43 • *This information is also present in Figure 1 and Table 2.*  
44
- 45
- 46 9. P8: please provide the ABIs in the HF and LF groups in the narrative
- 47
  - 48 • *Manuscript edited to include: "The LF-TENS group had a significantly lower mean ABI*  
49 *(0.57 vs 0.63, t(34) = 2.442)"*  
50
- 51
- 52 10. P8, L22-31: please provide some numbers in the narrative; I understand the desire not  
53 to repeat what's in the table but some measure difference would be helpful in the  
54 narrative
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  - 56
  - 57 • *Manuscript edited to include: "ICD, FCD and ACD results are detailed in Table 2.*  
58 *Compared to placebo TENS, median walking distance increased with TENS intervention*  
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2 *in both groups. This was true with the exception of FCD in the HF-TENS group (Mdn 187*  
3 *to 175m) and ICD in the LF-TENS group (Mdn 81 to 76m). All walking-related outcome*  
4 *measures changed with HF-TENS intervention. Only ACD changed with LF-TENS*  
5 *intervention (Mdn 179 to 288m,  $W_s = 39$ ,  $z = 2.025$ ,  $p = 0.043$ ,  $r = 0.48$ ). There was no*  
6 *change in MPQ-PRI scores for either group (Table 2)."*  
7  
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9  
10 11. P9: L50-53: did the authors attempt to adjust the analysis for differences in ABI?

- 11  
12 • *Due to the 'proof of concept' nature of the study and the limited sample size and*  
13 *statistical power this was thought to be beyond the scope of the current study.*  
14

15  
16 12. p11: The discussion of TM familiarization is a good one. Wouldn't the more logical  
17 design have been to allow the patient a practice test and then randomize the order?

- 18  
19 • *Most definitely. For future studies and when more resources are available this will be*  
20 *the design of choice.*  
21  
22 • *Manuscript edited to include: "Future studies should include treadmill familiarisation*  
23 *and employ a randomised order of entry, crossover design to more accurately explore*  
24 *the effect of TENS on walking performance in patients with IC." (Page 11)*  
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27  
28 13. Table 2: please indicate the units of measure and the final n for each group

- 29  
30 • *Table 2 edited as suggested.*  
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32 We look forward to your considered response.

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## TITLE PAGE

*Title:*

**Transcutaneous Electrical Nerve Stimulation (TENS) improves walking performance in patients with Intermittent Claudication (IC).**

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**What is new?**

- TENS may be a useful, cheap, safe and non-invasive adjunct intervention that facilitate walking and physical activity in patients with PAD and IC
- Two different modes of TENS were applied over the site of IC pain during a standardised graded treadmill test
- ICD and ACD increased with High Frequency-TENS but only ACD increased with Low Frequency-TENS, compared to Placebo TENS
- TENS intervention is associated with an increase in treadmill walking performance in patients with PAD and IC

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## Abstract

The purpose of this study was to investigate the effects of two types of Transcutaneous Electrical Nerve Stimulation (TENS) on walking distance and measures of pain in patients with Peripheral Arterial Disease (PAD) and Intermittent Claudication (IC). In a phase 2a study, forty participants with PAD and IC completed a graded treadmill test on two separate testing occasions. Active TENS was applied to the lower limb on the first occasion and placebo TENS on the second. Participants were divided into two experimental groups. One group received High-Frequency TENS (HF-TENS), the other Low-Frequency TENS (LF-TENS). Measures taken were: Initial Claudication Distance (ICD), Functional Claudication Distance (FCD) and Absolute Claudication Distance (ACD). The McGill Pain Questionnaire (MPQ) vocabulary was completed at the end of the intervention and the MPQ-Pain Rating Index (PRI) score calculated. Four participants were excluded from the final analysis due to non-completion of the experimental procedure. Median walking distance increased with HF-TENS for all measures ( $p < .05$ , Wilcoxon signed ranks test, all measures). Only ACD increased significantly with LF-TENS compared to placebo ( $Mdn = 179$  to  $228$ ,  $W_s = 39$ ,  $z = 2.025$ ,  $p = 0.043$ ,  $r = 0.48$ ). No difference was observed between reported median MPQ-PRI scores: 21.5 with placebo TENS and 21.5 with active TENS ( $p = .41$ ). TENS applied to the lower limb of patients with PAD and IC was associated with increased walking distance on a treadmill but not with any reduction in pain. TENS may be a useful adjunctive intervention to help increase walking performance in patients with IC.

## Keywords

Peripheral arterial disease, intermittent claudication, transcutaneous electrical nerve stimulation (TENS), ischaemic pain, exercise therapy

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## TEXT

### **Introduction:**

Peripheral Arterial Disease (PAD) is a clinical manifestation of atherosclerosis. Intermittent claudication (IC) is the most common manifestation, and is reported to affect between 10 and 30% of the population aged above 60 years of age.<sup>1</sup> PAD can be asymptomatic in the early stages, however as the disease progresses, the increasing atherosclerosis manifests as IC,<sup>2</sup> which is the cardinal symptom of PAD. IC is defined as pain in the lower limb(s) that is experienced during walking, and is relieved by rest.<sup>3,4</sup> Patients experiencing IC are characterised by reduced levels of daily physical activity, which is associated with diminished performance of personal, social and occupational activities of daily life. Many individuals become housebound or dependent on others<sup>5,6</sup> and studies suggest that patients with severe IC have a quality of life that equates to those with terminal cancer.<sup>7</sup>

The management of PAD and IC is primarily through the modification of risk factors, with endovascular intervention in severe cases and most medical therapies having only a modest benefit.<sup>8,9</sup> Exercise therapy, particularly supervised, is a mainstay of PAD and IC management that has been shown to have a significant effect on increasing walking distance, self-reported physical activity, measured cardio-respiratory fitness, exercise time and functional ability.<sup>3,10-16</sup> Despite the clear benefits of exercise therapy, over 45% of patients are non-compliant with healthcare professional advice to take regular exercise and to walk 'through' IC pain.<sup>11</sup> The pain associated with IC has been identified as a key barrier to walking.<sup>17</sup> Although acknowledged as a problem, there is little published literature examining analgesic interventions for IC pain.

Transcutaneous Electrical Nerve Stimulation (TENS) is a safe, inexpensive and non-invasive method of providing mild electrical stimulation for the relief of pain.<sup>18,19</sup> TENS has been reported to provide greater analgesic effects than placebo TENS for musculoskeletal,<sup>20</sup> postoperative<sup>21</sup> and neuropathic pain.<sup>22</sup> Packaged in a compact, portable unit that is easy to apply via small electrodes placed on the skin, a TENS unit can be kept unobtrusively in a pocket, or clipped to a trouser belt whilst being used to reduce pain and improve daily functioning.<sup>23</sup>

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4 However, thus far TENS has not been tested as a method of reducing pain and improving  
5 walking related function in patients with IC pain.  
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10 There are two main stimulation patterns, or dosages, of TENS employed in clinical practice:  
11 High-Frequency TENS (HF-TENS) and Low Frequency TENS (LF-TENS). Studies conducted to date  
12 suggest that the fast-acting, reflexive mechanism of HF-TENS may act most effectively at the  
13 mild (pain threshold) level of the pain experience. LF-TENS however may act most effectively at  
14 the stronger (pain tolerance) level of the pain experience due to extrasegmental but longer-  
15 lasting analgesic effects.<sup>23</sup>  
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23 In addition, although TENS has not been widely tested as a method of pain relief of IC, a  
24 previous investigation observed reductions in pain (hypoalgesia) with High Frequency TENS (HF-  
25 TENS) in healthy volunteers experiencing experimentally-induced ischaemic pain in the lower  
26 limb.<sup>24</sup> This may be due to the focus on exercise, and endovascular intervention as treatments  
27 for the condition and limited investigation into the nature of IC pain. Also the potential for high  
28 frequency verses low frequency patterns of TENS to affect different portions of the IC pain  
29 experience has not been examined.  
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39 We hypothesised that the two types of TENS might favourably, but differentially, affect discrete  
40 portions of the IC pain experience; for instance, when pain is mild (which normally occurs in  
41 PAD patients after walking a short distance), or when it becomes more severe (during  
42 continued walking). We therefore aimed to investigate the effects of HF and LF-TENS on  
43 measures of pain and walking performance in patients with PAD and IC.  
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4 **Material and Methods:**  
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6 *Participants:*  
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8 Ethical approval for the study was obtained from the NHS East of Scotland Research Ethics  
9 Service (Reference Number: 09/S1402/15). Forty participants with stable PAD and IC were  
10 recruited from the vascular outpatient clinic at Ninewells Hospital, Dundee, Scotland and block  
11 randomised into two experimental groups (HF-TENS and LF-TENS). Participants provided  
12 written informed consent and were included if they had: clinical diagnosis of PAD and stable IC  
13 of more than 3 months duration; Fontaine stage II claudication; resting Ankle Brachial Index  
14 (ABI) less than 0.90 in at least one leg; walking limited only by claudication; independent and  
15 safe mobility (no walking aids); were cognitively stable and able to follow instruction and were  
16 able to read and complete the questionnaires. Participants were excluded if they were: less  
17 than 40 years of age; had planned surgical or endovascular intervention for PAD; co-morbidities  
18 causing pain in the lower limb; ataxic gait or history of increased falls (unsafe for treadmill  
19 walking); myocardial infarction within the previous 6 months, cardiac arrhythmia or a cardiac  
20 pacemaker; current or previous sensation abnormalities in the lower limbs; epilepsy; medical  
21 diagnosis or self-reported psychiatric illness or previous experience of using TENS.  
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37 *Study Protocol:*  
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39 The experimental study design was a single blind, placebo-controlled, phase 2a, proof-of-  
40 concept trial. Each participant attended for two sessions, six to nine days apart with the  
41 majority of participants (n=30) completing both tests within seven days. A graded treadmill  
42 protocol<sup>25</sup> was completed by the participant at each. On the first occasion active TENS was  
43 applied and placebo TENS (P-TENS) on the second. For the purpose of blinding, the participants  
44 were told that “different ‘dosages’ of TENS were being tested, some of which may not be  
45 perceptible”. To enhance blinding and reduce the risk of bias, one researcher applied the TENS  
46 and a different researcher, who was blinded to the study protocol and the order of  
47 intervention, conducted the treadmill test and recorded the primary outcome measures.  
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58 *Treadmill Procedure:*  
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4 The treadmill procedure followed that described by Gardner et al <sup>25</sup> using a GE Marquette  
5 treadmill. Participants were connected to a 12-lead Echocardiograph (12-lead ECG) (GE CASE  
6 Premium Stress System), which recorded continuously throughout the procedure. A  
7  
8 familiarisation session was completed first where participants practiced walking at different  
9 speeds (1, 1.5 and 2mph) and the self-report method of rating claudication symptoms was  
10 explained. Further safety instructions were also issued: the participants were reminded to  
11 report any feelings of pain distinct from claudication and any feelings of dizziness/light-  
12 headedness immediately so that the test could be stopped. This series of events took less than  
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14 10 minutes to complete and the participant walked for a maximum of 30 seconds at each  
15 treadmill speed. Once this familiarisation procedure was completed, participants rested supine  
16 on a bed for 15 minutes in preparation for the full treadmill test.  
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27 *TENS Procedure:*

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29 A NeuroTrac 3™ TENS machine (Verity Medical Ltd, Surrey, UK) was fitted to the participant five  
30 minutes prior to each treadmill test and continued throughout the procedure. A segmental  
31 electrode application was employed using self-adhesive carbon rubber electrodes measuring  
32 5x5 cm (PhysioMed PALS® electrodes, Glossop, UK). The two electrodes were attached to the  
33 TENS unit via the manufacturer leads. The area of pain reported by the participant during the  
34 familiarisation session determined the electrode placement sites. The placement sites were at  
35 least 2cm apart. Electrodes were commonly placed with one proximal and one distal to the  
36 gastrocnemius muscle belly.  
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47 The TENS machine was calibrated prior to use with a digital oscilloscope and tested manually by  
48 the investigator prior to every testing session. The HF-TENS stimulation parameters were  
49 calibrated to 120Hz, pulse width 200µs and patient determined intensity of “strong but  
50 comfortable”. The LF-TENS stimulation was set at 2Hz, pulse width 200µs and patient  
51 determined intensity of “strong but comfortable and slight muscle twitch”.  
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4 The placebo TENS (P-TENS) condition used the same TENS model and programmed settings but  
5 with an inconspicuous break in the wires. This allowed the unit to be switched on with the  
6 appearance of a working unit but without any current reaching the participant. This was  
7 checked and confirmed with the use of an oscilloscope as described above.  
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14 *Measures:*

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16 Participants were instructed to report:

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18 1. When they first experienced claudication symptoms (Initial Claudication Distance (ICD))  
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21 2. When they reached the point at which they would usually stop walking (Functional  
22 Claudication Distance (FCD)) <sup>26,27</sup>  
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24 3. When they could not walk any further due to claudication symptoms (Absolute  
25 Claudication Distance (ACD)) <sup>25</sup>  
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31 Pain quality and intensity was recorded using a McGill Pain Questionnaire (MPQ); <sup>28</sup>  
32 administered 5 minutes after the participant completed the treadmill protocol. The MPQ  
33 consists of a vocabulary of adjectives from which the participant chooses appropriate words to  
34 describe the particular qualities of IC pain and accompanying feelings of distress and  
35 intrusion.<sup>29</sup>  
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43 *Statistical Analysis:*

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45 The mean scores for ICD, FCD and ACD were positively skewed and showed heteroscedascity. A  
46 log (10) transformation applied to normalise the data did not address the variance within the  
47 data, thus non-parametric statistics were used to analyse the data.  
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52 Wilcoxon Signed Ranks tests examined within-group differences in treadmill measures and  
53 MPQ-PRI scores. In order to reduce the effect of inter-participant variability, individual change  
54 in ICD, FCD and ACD between P-TENS and Active TENS was calculated for each participant.  
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57 **Distance walked with P-TENS was subtracted from the distance walked with Active TENS.** <sup>30</sup>  
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Individual percentage change was also calculated for ICD, FCD and ACD. The difference between the two sessions was calculated as a percentage of the distance walked with P-TENS. These values were then analysed using Mann-Whitney U tests for between-group comparisons. Statistical significance was set at  $p = 0.05$  (two-tailed) and analysis was performed using SPSS version 19.0.

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4 **Results:**

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6 *Participants:*

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8 Four participants were excluded from analysis due to non-completion of the experimental  
9 procedure. Three had previously unknown exercise-limiting co-morbidities and one was unable  
10 to walk safely on the treadmill. The remaining 36 participants (18 in each group) were included  
11 in the analysis (29 male, mean age (range) = 70 (54-87) years). Figure 1 summarises this  
12 information and displays the flow of participants through the study. The groups were similar in  
13 terms of demographic and disease data. The LF-TENS group had a significantly lower mean ABI  
14 (0.57 vs 0.63,  $t(34) = 2.442$ ) (Table 1).  
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24 *Within Group Profiles (HF-TENS and LF-TENS vs. P-TENS):*

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26 ICD, FCD and ACD results are detailed in Table 2. Compared to placebo TENS, median walking  
27 distance increased with TENS intervention in both groups. This was true with the exception of  
28 FCD in the HF-TENS group (Mdn 187 to 175m) and ICD in the LF-TENS group (Mdn 81 to 76m).  
29 All walking-related outcome measures changed with HF-TENS intervention. Only ACD changed  
30 with LF-TENS intervention (Mdn 179 to 288m,  $W_s = 39$ ,  $z = 2.025$ ,  $p = 0.043$ ,  $r = 0.48$ ). There was  
31 no change in MPQ-PRI scores for either group (Table 2).  
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40 *Between Group Profiles (HF-TENS vs. LF-TENS):*

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42 There was an overall increase in all measures in both groups as shown by the positive change  
43 values in Figures 2 and 3. The only difference between the groups was in change and  
44 percentage change in ICD (Mdn (IQR) = 26 (71) with HF-TENS and 6 (67) with LF-TENS,  $U = 268$ ,  $z$   
45 = 2.073,  $p = 0.038$ ,  $r = 0.49$  and Mdn (IQR) = 43 (64) with HF-TENS and 9 (79) with LF-TENS,  $U =$   
46 267,  $z = 2.088$ ,  $p = 0.037$ ,  $r = 0.49$  respectively) (Figures 2 and 3).  
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4 **Discussion:**  
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6 The results of this study indicate that compared to placebo, the application of TENS whilst  
7 walking on a treadmill is associated with a modest but statistically significant improvement of  
8 walking performance in patients with IC. These results indicate that TENS offers potential as a  
9 clinically useful intervention that allows patients with IC to walk further before onset of pain,  
10 and while experiencing pain.  
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18 The two different stimulus patterns of TENS employed in this study were found to affect  
19 distinctive aspects of the pain experience. ICD and ACD increased with HF-TENS whereas only  
20 ACD increased with LF-TENS. The different stimulus patterns of HF-TENS and LF-TENS appear to  
21 have activated different mechanisms of hypoalgesia and distinct neurophysiological effects.  
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27 Increases in ICD and ACD were observed in the HF-TENS group suggesting an immediate and  
28 prolonged hypoalgesic effect. Median FCD decreased with HF-TENS intervention however, this  
29 appeared to be due to the large variance within the sample, as illustrated by an increase in IQR  
30 (Table 2). Also, when correcting for baseline ability (change scores, Figure 2), median FCD was  
31 found to be greater than zero therefore indicating an overall increase in walking distance. The  
32 increases in median ICD and ACD with HF-TENS were found to be significant with effect sizes of  
33 .69 ( $p = .004$ ) and .53 ( $p = .025$ ) respectively (Table 2 and Figures 2 and 3). In the LF-TENS group,  
34 there was a decrease in median ICD but increases in FCD and ACD suggesting a delayed but  
35 effective hypoalgesic effect at pain tolerance. The increase in ACD with LF-TENS was found to  
36 be significant with an effect size of .48 ( $p = .043$ ) (Table 2). These findings suggest that HF-TENS  
37 had an immediate and lasting effect; increasing walking distance at the mild (ICD) and more  
38 severe phases of the pain experience (ACD). The effects of LF-TENS however, were only evident  
39 when the pain was severe (ACD) indicating a delayed action. These results must be interpreted  
40 with caution as the significantly lower ABI in the LF-TENS group indicates more severe PAD  
41 which could have contributed to the poor response. A further variable is the sequencing of the  
42 placebo after the TENS treatment which could have un-blinded the study for the participants  
43 and led to less of a response when no stimulation was perceived.  
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6 HF-TENS is proposed to act by activating large diameter mechanoreceptors (A $\beta$ -fibres), delta  
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8 ( $\delta$ )-opioid receptors and increasing gamma-Aminobutyric acid (GABA) in the spinal cord. It is  
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10 associated with immediate, localised, segmental inhibition as conceived by the original gate  
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12 control theory.<sup>31,32</sup> LF-TENS was originally theorised to act on smaller diameter nociceptive  
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14 afferents, brainstem structures and supraspinal descending pathways, releasing endogenous  
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16 opiates centrally and peripherally.<sup>32,33</sup> In contrast to HF-TENS, it was thought that LF-TENS did  
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18 not induce immediate hypoalgesia but had a latent effect of pain relief due to its more complex  
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20 mechanisms.<sup>34</sup> These differential mechanisms of action have recently been challenged.<sup>35</sup>  
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22 Nevertheless, the originally proposed mechanisms of action would explain the characteristics of  
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24 hypoalgesia evident in the current study.

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27 Our 'proof of concept' results indicate that HF-TENS improved walking performance during the  
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29 period of treadmill walking that would normally correspond with the first appearance of IC pain  
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31 and when it is growing in intensity. In contrast, LF-TENS did not appear to affect walking  
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33 performance in those portions of the walking exercise. Instead, the effect of LF-TENS  
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35 corresponds with that later period of treadmill walking when IC pain would normally be most  
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37 severe and intolerable.

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41 There is no consensus in the literature regarding modification of which aspect of the IC pain  
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43 experience (ICD, FCD or ACD) results in the greatest gains in walking performance and therefore  
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45 the most effective management. From the results of the current study it would seem that HF-  
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47 TENS might be more effective due to the hypoalgesic effects evident throughout the pain  
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49 experience. These conclusions however are tentative and future investigations could further  
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51 explore the relationships between the IC pain experience and different applications of TENS.

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55 Pain relief is thought to be the primary action of TENS however, neither TENS group reported  
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57 any change in MPQ-PRI scores. Whereas the results suggest that pain intensity was not  
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59 affected, an alternative explanation could be related to the experimental methodology. The  
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4 MPQ was completed at the end of the treadmill test and participants were asked to describe  
5 their pain at ACD. The participants were therefore walking to the same level of pain intensity on  
6 both occasions. As discussed above, ACD increased with both types of TENS intervention and  
7 thus, even though there was no change in maximum pain intensity, the distance walked before  
8 ACD was reached was greater when using TENS compared to placebo. This result indicates that  
9 TENS, rather than masking and reducing the experience of maximum pain in patients walking  
10 with IC pain, prolongs the time taken to reach pain tolerance. This finding is in line with results  
11 of our experimental study of TENS for laboratory-induced lower limb ischaemic pain in healthy  
12 volunteers.<sup>24,36</sup>  
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23 Compared to P-TENS, the median change in ACD with HF-TENS was 30 metres (m) and with LF-  
24 TENS, 23m. This relates to percentage increases of 13% for HF-TENS and 18% with LF-TENS  
25 (Table 3 and Figure 3). A 60% improvement in ACD has been suggested as a functionally  
26 significant improvement in walking distance for patients with IC.<sup>37</sup> The observed effect of TENS  
27 on walking performance in the current study, conducted within the operational constraints  
28 imposed by a routine PAD clinic setting, was such that one might anticipate a degree of  
29 'dampening' of the potential effect of TENS. A familiarisation or training effect has been shown  
30 with the Gardner treadmill test.<sup>38</sup> Cognisant of this fact, P-TENS condition was examined on the  
31 second testing session for every participant. By the nature of this design, any effect of TENS  
32 observed would be masked by the potential accommodation effect during the second treadmill  
33 test. The training/accommodation effect for the Gardner treadmill protocol has been found to  
34 be 15% for ACD.<sup>38</sup> With this in mind, the significant increases of 13% and 18% with HF and LF-  
35 TENS may become closer to a clinically worthwhile improvement. IC medication is associated  
36 with an increase of approximately 30% compared to placebo.<sup>39</sup> The change in ACD with TENS  
37 intervention, taking into account the possible treadmill walking accommodation effect (10%) is  
38 close to this level of improvement (increase of 23% and 28% compared to placebo). Future  
39 studies should include treadmill familiarisation and employ a randomised order of entry,  
40 crossover design to more accurately explore the effect of TENS on walking performance in  
41 patients with IC.  
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6 This study makes a novel contribution to the literature on the management of PAD and IC.  
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8 There is no previously published report of the effect of TENS on walking performance and pain  
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10 in this patient population. Our clinical results are also supported by our previous publication on  
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12 HF-TENS for ischaemic pain in healthy volunteers.<sup>24</sup> However this is a 'proof of concept' study.  
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14 Further study could examine the effectiveness of TENS as an adjunctive intervention for walking  
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16 performance in patients with IC in more detail. For example, further investigation is required  
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18 that examines the effects on pain, haemodynamic changes and gait during treadmill walking.  
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20 There is also a need for investigations that explore the effects of TENS on IC-limited walking in  
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22 people with PAD during more ecologically valid (over ground) walking tasks.  
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26 *Limitations:*

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28 One aspect of the current study that could be viewed as a limitation is the lack of a no-TENS  
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30 control group. By neglecting to include a no-TENS control condition it was not possible to  
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32 accurately quantify the effect of the placebo effect of TENS. It has been proposed that part of  
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34 the beneficial effect of TENS is the sense of 'control' and the perception of receiving an  
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36 'intervention' experienced by patients when applying the device. Without a no-TENS group this  
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38 effect cannot be quantified. The study was designed as a proof-of-concept, MRC Phase 2a trial  
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40 and a pragmatic approach was assumed. When investigating the effects of TENS with the aim of  
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42 evaluating physiologically quantifiable outcomes, TENS must demonstrate efficacy above  
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44 placebo therefore the current study design is sufficient. Nevertheless, future studies should  
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46 include a no-TENS control to allow investigation of the placebo response to TENS in PAD and IC.  
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50 Another possible limitation of this study was the ordering of intervention. As the treadmill test  
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52 with active TENS preceded the application of placebo for all participants, any effect of TENS  
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54 observed could be temporal. This design was selected to account for participant familiarisation  
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56 with the treadmill test. Previous research has indicated that participants commonly walk  
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58 approximately 15% further during subsequent graded treadmill tests<sup>37</sup>. What this design  
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60 achieves is that any signal detected (i.e. an increase in walking distance with TENS) must have  
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4 first exceeded the 'noise' of familiarisation. Overall, this design 'handicapped' the study and  
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6 ensured that any findings are more cautious.  
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10 *Conclusions:*

11 Patients with IC experience a gradual build-up of pain to tolerance when exercising until the  
12 pain becomes intolerable. The current study aimed to investigate the effects of two types of  
13 TENS (high and low frequency) on the pain experienced and walking performance in patients  
14 with PAD and IC. The results indicate that TENS increases the distance walked before tolerance.  
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16 Both types of TENS were found to increase walking performance but HF-TENS was more  
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18 effective at prolonging the time to reach pain threshold.  
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Table 1: Demographic and baseline data for all participants. *p* values relate to independent student's t-tests (two tailed) of the group values

Table 2: Median (IQR) ICD, FCD and ACD (in metres) and MPQ-PRI scores for both groups with placebo and with TENS intervention

Figure 1: CONSORT diagram displaying the progression of participants through the study.

Figure 2: Boxplots representing change in walking measures (metres) with TENS intervention in both groups. Positive values represent a positive change with TENS intervention over placebo.

Figure 3: Boxplots representing percentage change in walking measures with TENS intervention in both groups. Positive values represent a positive change with TENS intervention over placebo.

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Table 1

Characteristic	All		Group				<i>p</i> value
	Mean	SD	HF-TENS		LF-TENS		
	Mean	SD	Mean	SE	Mean	SE	
Age (years)	70	8.0	68	1.8	71	1.9	0.344
BMI (kg/m <sup>2</sup> )	28	4.2	29	1.0	27	1.0	0.261
HR (bpm)	71	9.4	71	2.0	71	2.4	0.986
BP (sys) (mmHg)	146	18.1	147	5.2	146	3.2	0.943
ABI (AU)	.63	.164	.70	.041	.57	.031	0.020*
ICD (m)	86	51.7	85	15.5	88	8.1	0.867
FCD (m)	202	127.1	222	32.4	182	27.4	0.351
ACD (m)	259	169.2	268	39.4	250	41.4	0.750
MPQ-PRI (0-78)	21	7.9	20	1.9	23	1.8	0.219

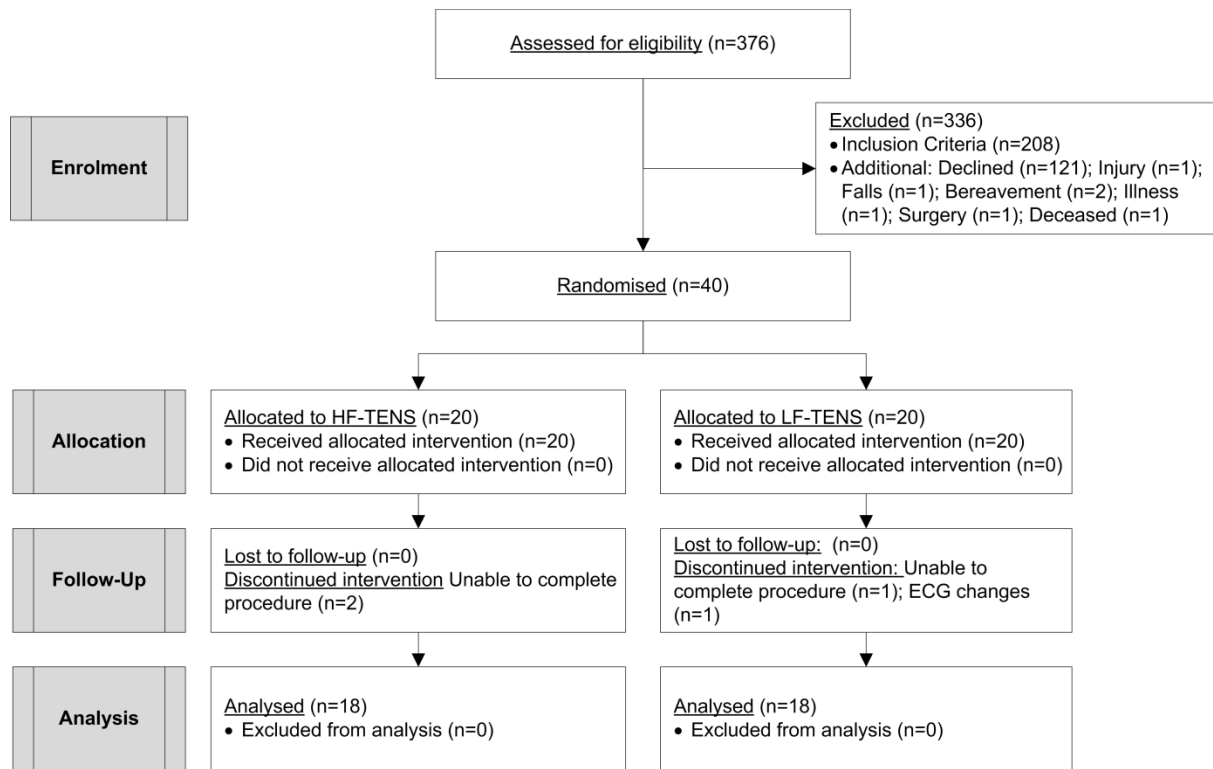
BMI = body mass index; HR = heart rate; BP (sys) = systolic blood pressure;  
ABI = ankle brachial index (measured in arbitrary units (AU)); ICD = initial claudication distance; FCD = functional claudication distance; ACD = absolute claudication distance;  
MPQ-PRI (0-78) = McGill pain questionnaire pain rating index



Table 2

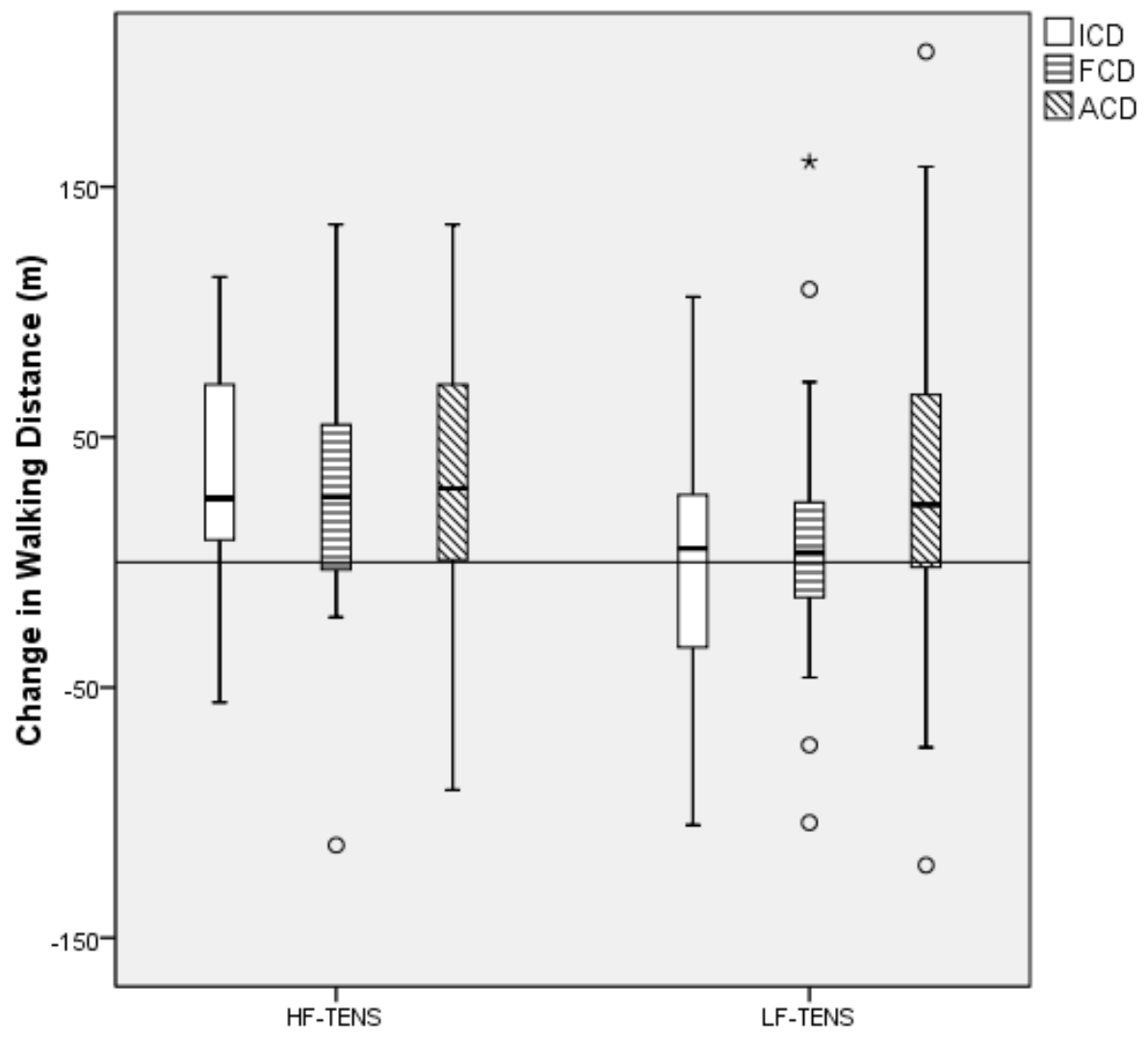
			Placebo	Intervention	<i>p</i>	<i>W<sub>s</sub></i>	<i>r</i>
1	<b>HF-TENS Group</b> ( <i>n</i> = 18)	<b>ICD (m)</b>	61 (68)	82 (112)	.004*	18	.69
2		<b>FCD (m)</b>	187 (175)	175 (303)	.025*	34	.53
3		<b>ACD (m)</b>	211 (244)	212 (297)	.025*	34	.53
4		<b>MPQ-PRI (au)</b>	19 (8.5)	24 (13.3)	.476	48	.17
5	<b>LF-TENS Group</b> ( <i>n</i> = 18)	<b>ICD (m)</b>	81 (38)	76 (50)	.965	85	.01
6		<b>FCD (m)</b>	151 (130)	158 (114)	.687	62	.16
7		<b>ACD (m)</b>	179 (153)	228 (218)	.043*	39	.48
8		<b>MPQ-PRI (au)</b>	24 (11.5)	21 (17)	.601	74	.12
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Figure 1



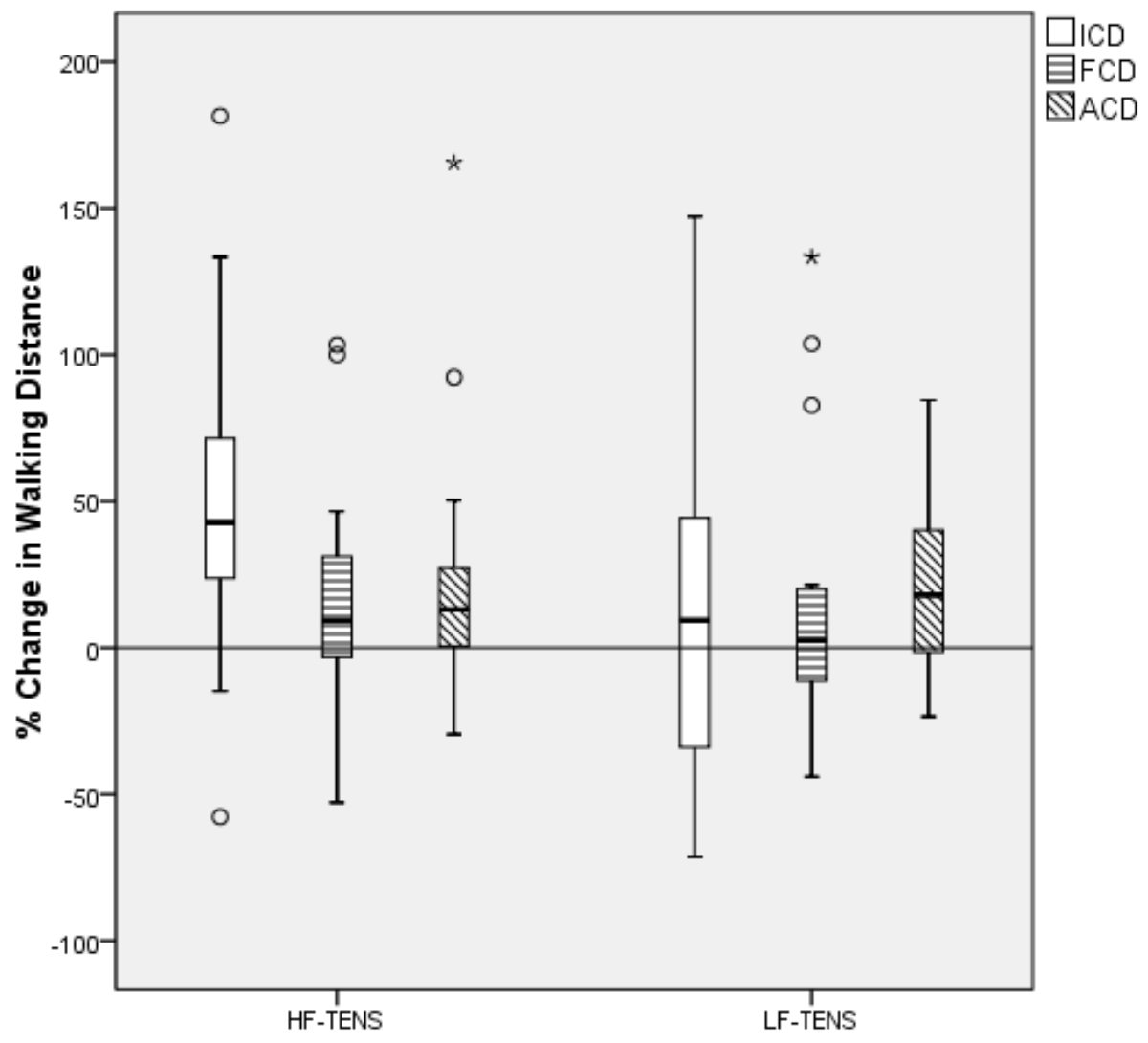
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