Journal of Integrative Neuroscience

*J. Integr. Neurosci.* **2022**; 21(2): 053
https://doi.org/10.31083/j.jin2102053

*Original Research*

# Blood flow restriction exercise of the tibialis anterior in people with stroke: a preliminary study

Simon Svanborg Kjeldsen[1], Erhard Trillingsgaard Næss-Schmidt[1], Michael Lee[2,3], Camila Quel de Oliveira[4], Jørgen Feldbæk Nielsen[1], Peter William Stubbs[1,4,*]

[1]Research Department, Hammel Neurorehabilitation and Research Center, Aarhus University, 8450 Hammel, Denmark
[2]Discipline of Physiotherapy, School of Health, Federation University, 3841 Victoria, Australia
[3]Faculty of Medicine and Health, School of Health Sciences, University of New South Wales, Sydney, 2052 NSW, Australia
[4]Graduate School of Health, Discipline of Physiotherapy, University of Technology Sydney, Sydney, 2007 NSW, Australia
*Correspondence: peter.stubbs@uts.edu.au (Peter William Stubbs)
Academic Editor: Emilia Salvadori
Submitted: 31 August 2021 Revised: 15 September 2021 Accepted: 27 December 2021 Published: 21 March 2022

**Abstract**

**Background**: Blood flow restriction exercise (BFR-E) could be a useful training adjunct for patients with weakness after stroke to augment the effects of exercise on muscle activity. We aimed to examine neurophysiological changes (primary aim) and assess patient perceptions (secondary aim) following BFR-E. **Methods**: Fourteen participants with stroke performed BFR-E (1 session) and exercise without blood flow restrictsion (Exercise only) (1 session), on two days, ≈7 days apart. In each session, two sets of tibialis anterior (TA) contractions were performed and electromyography (EMG) was recorded. Eight participants underwent transcranial magnetic stimulation (single-pulse stimulation, short interval intracortical inhibition (SICI), intracortical facilitation (ICF)) and peripheral electrical stimulation (maximal peak-to-peak M-wave (M-max)) of the TA before, immediately-after, 10-min-after and 20-min-after BFR-E and Exercise only. Numerical rating scores (NRS) for pain, discomfort, fatigue, safety, focus and difficulty were collected for all subjects (n = 14). Paired comparisons and linear mixed models assessed the effects of BFR-E and Exercise only. **Results**: No adverse events due to exercise were reported. There was no contraction-number × condition interaction for EMG amplitude during exercise ($p = 0.15$), or time × condition interaction for single-pulse stmulation, SICI, ICF or M-max amplitude ($p = 0.34$ to $p = 0.97$). There was no difference between BFR-E and Exercise only in NRS scores ($p = 0.10$ to $p = 0.50$). **Conclusion**: Using our training paradigm, neurophysiological parameters, feasibility, tolerability and perceptions of safety were not different between BFR-E and Exercise only. As participants were generally well-functioning, our results are not generalizable to lower functioning people with stroke, different (more intense) exercise protocols or longer term training over weeks or months.

**Keywords:** Intracortical inhibition; Intracortical facilitation; Strength training; Motor cortex; Tibialis anterior; Plasticity; Occlusion training; Transcranial magnetic stimulation

## 1. Introduction

Strength training and repetitive task-specific training are important for regaining voluntary motor control, independence and promoting functional recovery after stroke [1,2]. As recovery following stroke is time-dependent [3], it is important to ensure that the maximal possible training benefit is achieved in the least possible time, so that patients have time and opportunity to address any other impairments they may encounter following a stroke. Despite rehabilitation efforts, most stroke survivors do not fully regain strength and therefore face life-long disability [4]. Given this, strategies to enhance the efficiency and efficacy of strength training are essential to improve functional outcomes of people with stroke.

Blood flow restriction training is a training strategy used in healthy people, and has been proposed in elderly people, people following surgery [5] and neurological populations. The cardiovascular changes when exercising with blood flow restriction are widespread and include local and systemic mechanisms (see [6] for review). However, there is a complex interplay between the vascular and neurological system. Changing cardiovascular parameters can directly affect the metabolites within the blood and blood flow to the brain, via the blood brain barrier [7]. Furthermore, by occluding blood flow at the limbs, sensory and motor nerves are affected distal to the blood pressure cuff, and preferentially derecruited, depending on the cuff pressure and the length of time under blood flow restriction [8]. Given this, blood flow restriction, even though apparently influencing the cardiovascular system, can have widespread neurological effects.

In healthy elderly people, exercise regimes using blood flow restriction (BFR-E) increase muscle size, strength and function compared to Exercise only (E-only) regimes [9–12]. Due to the proposed benefits, BFR-E has been prescribed for people following Anterior Cruciate Ligament (ACL)/orthopaedic surgery [13–16], adults with osteoarthritis [15,17], rheumatoid arthritis [15] and

patellofemoral pain [14–16] to reduce pain and increase strength and function.

Although used in musculoskeletal populations, experimental studies applying BFR-E in people with stroke are sparse [18]. Despite this, a Japanese national survey showed that 11% of the Japanese rehabilitation clinics that use blood flow restriction (BFR), are using it in patients with stroke, presumably with the aim of optimising strength training and motor recovery [19,20]. Moreover, BFR-E has also been investigated in people with other neurological disorders including Multiple Sclerosis [21–25] and incomplete Spinal Cord Injuries (SCI) [26–31], with most (not all [24,30]) studies showing that BFR-E was safe and increased muscle strength, size and function. One case study reported one event of symptomatic autonomic dysreflexia and three events of asymptomatic autonomic dysreflexia with BFR-E training in an individual with SCI, over a 4-week training period [30]. This case study highlights the importance of patient selection and screening, prior to commencing BFR-E, to ensure no pre-existing conditions are exacerbated by BFR-E [30]. Despite that study [30], in all other surveys/studies, BFR-E appears to be safe and well tolerated with very few adverse events reported.

In people with stroke, a small randomised controlled study, reported at a conference, compared the effects of arm crank ergometry with and without BFR in 10 participants for 10 weeks 1×/day, 4 days/week [18]. Following training, the BFR-E group demonstrated greater improvements in motor function as measured by the Fugl-Meyer upper extremity score and the Box and Block test in comparison to the E-only group. Although positive, details on randomisation, concealment and blinding were not reported, and therefore, caution is required when interpreting these results.

As neurological patients have been rarely investigated in BFR-E protocols, there is a lack of understanding on the neurological mechanisms underlying its potential effects in these patients. In healthy subjects, single sessions of BFR-E reduced single pulse motor evoked potentials (MEP)s in multiple muscle groups, for 20 to 30 minutes [32–38], indicating central fatigue. However, some studies have shown no post-exercise differences between BFR-E and E-only [39]. Paired pulse paradigms investigating short interval intracortical inhibition (SICI, interstimulus intervals of 2–3 ms) and intracortical facilitation (ICF, interstimulus intervals of 10–15 ms) have also shown no differences between BFR-E and E-only paradigms for SICI [39,40] and ICF [39]. SICI can provide an indication of cortico-cortical inhibition due to Gamma-aminobutyric acid (GABA) mediated pathways [41–45] and while the mechanisms of ICF aren't completely known it has been proposed that it provides an indication of the efficacy of cortico-cortical facilitation due to glutaminergic pathways [46–49].

Although previous transcranial magnetic stimulation (TMS) studies in healthy people showed minimal differences in SICI and ICF between BFR-E and E-only, there is little information about the cortical effects of BFR-E following a stroke. This is an area worthy of further investigation given that there are well-document changes to the balance of cortical facilitation and inhibition after stroke [49]. For example, people with stroke have shown impaired GABA regulation and reduced GABA mediated inhibition. Furthermore, in the early phases of rehabilitation there is less SICI in the ipsilesional [49,50] and contralesional hemispheres [46], where more GABA mediated disinhibition in ipsilesional and contralesional hemispheres appear to favour functional recovery [50,51]. As high pressure BFR alone can temporarily reduce cortical GABA concentrations [52] and increase the size of motor volleys to deafferented muscles [53], it is possible that BFR could be used as a primer to alter cortical excitability and may augment the benefits of training/exercise. Moreover, chronic stroke patients, whose GABA concentrations reduced during E-only, showed greater improvements in function following 2 weeks of constraint induced movement therapy [54]. As such, it is possible that exercise in combination with BFR could assist in reducing GABA mediated inhibition and facilitate motor recovery. Although current evidence suggests that ICF does not change following stroke [49,51], it can change following exercise (independent of BFR) in people with chronic stroke [55] and healthy people [39].

Considering the potential benefits of BFR-E in optimising muscle strength and recovery after stroke, the purpose of the current study was to trial a low pressure (0.8 × systolic blood pressure) single session of BFR-E in comparison with a single session of E-only in people with mild dorsiflexor weakness following stroke. The dorsiflexors were chosen as (1) it is easy to occlude proximal to the tibialis anterior (at the thigh), (2) it is a muscle that is frequently weak in people with stroke and (3) it is easier to attain TMS responses in the tibialis anterior, compared to other lower limb muscles.

The primary aims were to assess if the muscle activity was different between BFR-E and E-only during exercise and to determine if post-exercise neurophysiological measures (single pulse TMS, SICI, ICF and M-max amplitude) were different between 1 session BFR-E and 1 session E-only. The secondary aim was to determine if patient perceptions of pain, discomfort, fatigue, safety, focus and difficulty of exercise were different between BFR-E and E-only to ultimately assess if BRF-E is feasible and tolerated in stroke populations. To our knowledge, this is the first study to specifically train the ankle dorsiflexors in people with stroke using BFR-E. For the adoption of BRF-E into rehabilitation practice, we must understand whether participants will tolerate and be accepting of this training modality.

## 2. Materials and methods

### *2.1 Subjects*

We consecutively recruited stroke patients over a 13 month period from October 2016 to November 2017. For this preliminary study, our recruitment target was 16 patients [56]. This sample size would provide us with an indication of neurophysiological effects of BFR-E as well as provide information about the feasibility and tolerability of BFR-E. Fifteen participants were recruited and 14 participants completed training (see Table 1 for participant characteristics).

### *2.2 Inclusion and exclusion criteria*

Participants were included if they (a) were 18 to 80 years old, (b) had been discharged from acute hospitalisation, (c) had a first time ischemic or haemorrhagic stroke of any chronicity, (d) could walk 10 m with or without a walking aid, (e) had manual muscle test scores of $\geq$3 in the tibialis anterior (f) were able to attend the exercise sessions, (g) were medically stable, (h) were able to communicate verbally and (i) could speak Danish or English. Patients were excluded if they had (a) resting systolic blood pressure $>$160 mmHg or resting diastolic blood pressure $>$100 mmHg, (b) evidence of lower limb peripheral oedema, (c) open wounds or fragile skin, (d) cognitive deficits preventing the participants from undergoing the assessments, exercise program or informed consent process, (e) major neurological/musculoskeletal deficits that could affect training, that were unrelated to the stroke, (f) administration of botulinum toxin in the lower limb at least 6 months prior to training, (g) history of epilepsy, (h) cochlear implants, (i) a pacemaker, (j) any type of deep brain stimulator and (k) metal implants in the head or neck. Participants were not excluded from the study if they did not have motor evoked potentials using TMS as they could still provide information to answer our other aims (muscle activity during training, M-Max amplitude and NRS scores).

### *2.3 Neurophysiological measures*

Surface electromyography activity (sEMG) were recorded using (Ambu Neuroline) surface electrodes. Electrodes were placed on the muscle belly of the tibialis anterior in accordance with previous recommendations [57]. sEMG data were amplified using custom built amplifiers and band pass filtered from 10 Hz to 500 Hz recorded at a sampling rate of 4 kHz. TMS was delivered using a magnetic stimulator (Magstim 200, Magstim Company Ltd, United Kingdom) using a 110 mm double cone coil. Data were collected and stimuli were controlled using custom-made software (Mr Kick II) as has been used previously [58]. Brachial blood pressure was measured using a sphygmomanometer (Riester® 55 cm $\times$ 14.5 cm) and blood flow restriction was performed using one of two blood pressure cuffs, depending on the size of the thigh (Reister® 70 $\times$ 22 cm or Reister® 100 $\times$ 26 cm).

TMS and peripheral electrical stimulation were collected prior to exercise (T0), immediately after exercise (T1), 10 min after exercise (T2) and 20 minutes after exercise (T3). During testing at each time, peripheral electrical stimulation measurements always preceded TMS measurements.

#### 2.3.1 Peripheral electrical stimulation

The process for establishing thresholds and determining peripheral electrical stimulus intensity has been described elsewhere [39,58]. Briefly, 100 $\mu$s single rectangular pulses were delivered at the head of the fibula with stimuli delivered every 2–2.5 seconds. The stimulus intensity was increased when further increasing the stimulus intensity did not increase the peak-to-peak M-wave (M-max). For testing, the intensity that elicited M-max was delivered every 2–2.5 s for 10 stimuli per time point.

#### 2.3.2 Cortical assessment using transcranial magnetic stimulation (TMS)

The process for establishing thresholds and determining TMS stimulus intensity has been described elsewhere [39,58]. Briefly, patients were lying and wore a non-stretchable fabric cap that remained on the head during testing. Current was applied in the anterior to posterior direction. The approximate hotspot was determined by systematically moving and stimulating locations on the scalp (every 5–7 seconds) at the approximate location of the hotspot. To find the hotspot, an intensity of 50% of the maximal stimulator output (MSO) was initially used. As some patients had no discernible MEPs at 50% of the MSO in any scalp location, the process was repeated for stimulus intensities of 55% and 60% of the MSO. If a patient had no discernible MEP at 60% of the MSO, no further TMS was performed, but patients continued with peripheral electrical stimulation and exercise. This is because the paired pulse stimulation protocol for patients with resting motor thresholds rMT(s) $>$60% of the MSO was deemed too uncomfortable by the investigators. The hotspot was determined as the scalp location that produced the maximum peak-to-peak MEP in the tibialis anterior. This was marked as the location for all further TMS testing for that session. Following this, the stimulus intensity was reduced to 35% of the MSO. At this intensity, stimuli were delivered and the intensity was increased by 5% of the MSO until $\geq$5/10 MEPs in the tibias anterior had a peak-to-peak amplitude of $>$50 $\mu$V. This intensity was deemed the rMT. The process was performed separately for each session. For testing, single pulse stimulation was delivered at 120% of the rMT. Paired pulse stimulation was delivered at 80% (conditioning stimulus) and 120% (test stimulus) of the rMT, at interstimulus intervals of 2 ms (SICI) and 15 ms (ICF). During testing, single and paired pulse stimuli were delivered randomly every 5–7 seconds for 12 stimuli per testing time point.

*2.4 Numerical rating scale*

Patients provided a numerical rating for their perceptions of pain, discomfort, difficulty and fatigue during exercise with 0 indicating no pain, discomfort or fatigue and 10 indicating the highest imaginable pain, discomfort or fatigue. Patients were also asked about how safe and focused they felt during exercise with 0 indicating feelings of being unsafe and unfocussed and 10 indicating feelings of being safe/focused.

*2.5 Experimental procedures*

Fig. 1 provides an overview of the experimental procedures. Prior to day 1, an investigator explained the experimental procedures to participants via phone or in person and participants were sent/provided a copy of the participation information sheet and consent form. On day 1, an investigator discussed the project with the participant and acquired written informed consent. In the initial consultation and prior to testing, participants were screened against the inclusion and exclusion criteria. Demographic and clinical data were collected and included: age, sex, time since stroke, stroke location, dominant leg, height, mass, 10-meter walk test time, modified Ashworth score of the plantarflexors and dorsiflexors (in lying with the knee straight), manual muscle testing of the plantarflexors and dorsiflexors (in lying with the knee straight) and brachial blood pressure (measured on both days in lying on the less affected arm). If participants were not suitable for testing based on these measures, no further questioning/testing was performed. Following testing and after eligibility was determined, the session performed first (BFR-E or E-only) was drawn randomly from an envelope. Depending on randomization, participants performed E-only or BFR-E in the first session, with the other condition performed in the second session. Sessions were spaced 7 $\pm$ 1 day(s) apart. Seven days between sessions was chosen as the patients would unlikely change functional status in this time and unlikely have any carryover effects from the first session. As such, any post-exercise fatigue as a result of the first training session would have completely subsided by the second session.

After thresholds had been established, T0 measurements for TMS and peripheral electrical stimulation were collected. For all participants, sEMG electrodes were affixed and sEMG data were collected during training.

During training, patients were seated comfortably. The foot was relaxed and resting on a board at an average ankle angle of 118 $\pm$ 12° (mean $\pm$ SD) and an average knee angle of 109 $\pm$ 10°. From this position, the maximum comfortable dorsiflexion range for each subject was determined. A target was placed at this location during testing. Following this, subjects placed their foot under a TheraBand affixed to the board (for stronger patients) or no TheraBand (for weaker patients) and asked to lift the foot to the target. The target was placed within the range of motion of the ankle joint. Patients practiced 4–5 times while timing

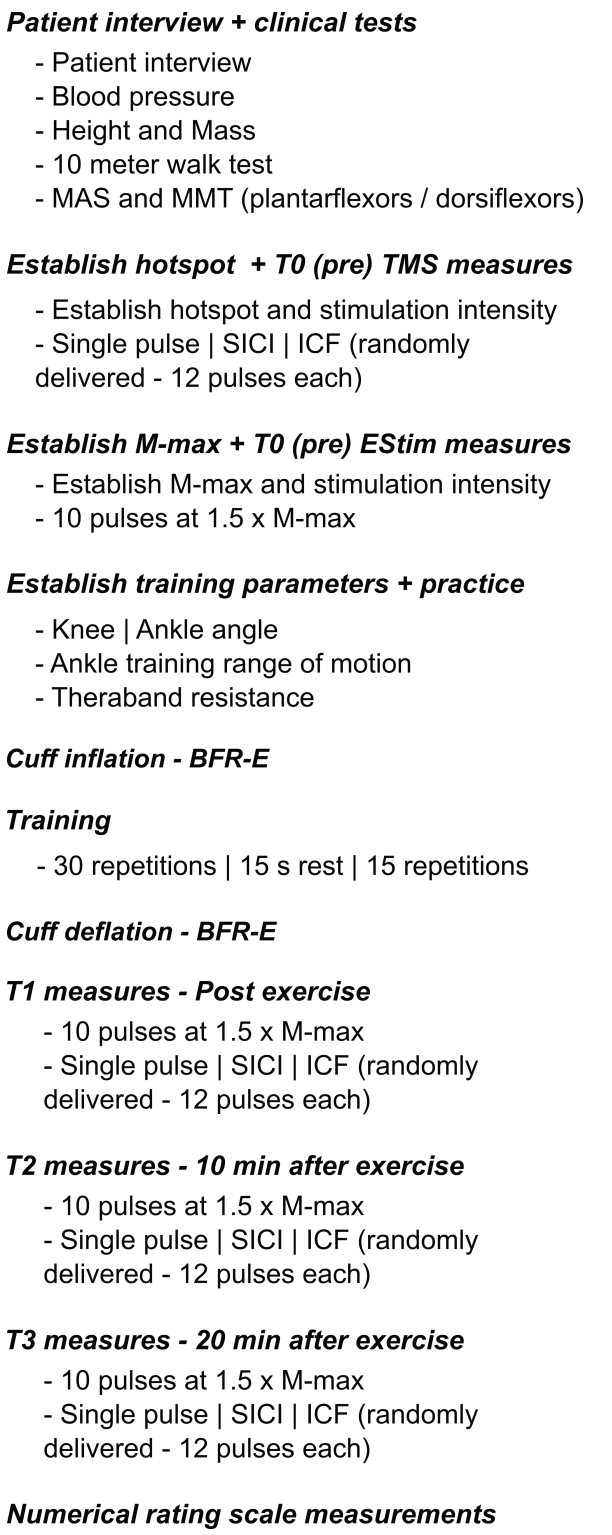


**Fig. 1. Overview of the experimental procedures.** Abbreviations included in the figure: MAS, modified Ashworth scale; MMT, Manual Muscle test; M-max, Maximal peak-to-peak M-wave; EStim, Peripheral electrical stimulation; SICI, Short interval intracortical inhibition; ICF, Intracortical Facilitation; BFR-E, Exercise with Blood Flow Restriction; E-only, Exercise without Blood Flow Restriction; rMT, resting Motor Threshold.

the contraction to a metronome and adjustments to the set up were made, as required. Once subjects were comfortable, the knee and ankle angle were measured to facilitate testing in the same position between days.

During training, participants performed one set of 30 repetitions and one set of 15 repetitions of dorsiflexion, with 30 seconds rest between sets. This is a reduced exercise paradigm from blood flow restriction paradigms that have been used previously [39,40,59,60]. Participants concentrically contracted the TA for ≈1 s, held the foot at the stop for ≈2 s and lowered the foot over ≈0.5 s. Some participants fatigued and were unable to reach the target at the end of training. If this occurred, participants were asked to dorsiflex the foot as much as able in time with a metronome.

For BFR-E, the blood pressure cuff was placed around the thigh and inflated over 1 min to 0.8 × systolic blood pressure, as performed previously. Exercise commenced when the testing pressure had stabilised. Pressure was monitored during testing and adjusted if needed.

Following training, participants that were eligible for TMS and M-wave measurements received these at T1, T2 and T3. Participants that did not received these, waited for 20 min before answering the numerical rating scales of the exercise session. For these questions, patients were asked only to comment on the exercise itself and not the neurophysiological testing, if performed.

### *2.6 Data analysis*

For sEMG during training, the amplitude of the sEMG measurements during exercise for each contraction were measured. Post data collection, data were smoothed using a 1st order, 1 Hz low pass Butterworth filter. Contraction onset threshold was 25 $\mu$V. A contraction was determined when the sEMG exceeded the threshold for at least 20 ms and the contraction lasted for at least 1.5 seconds. sEMG amplitude was the root mean square (RMS) measured in the 1.5 seconds following the contraction onset. The RMS amplitude was averaged in blocks of 5 contractions, for a total of nine contraction blocks (45 total contractions).

The amplitude of M-wave and MEPs was taken as the peak-to-peak amplitude ($\mu$V) of the raw EMG traces from 3 ms to 33 ms after the stimulus for the M-wave and 25 to 70 ms after the test stimulus for MEPs. These time windows encompassed the peak-to-peak responses for all subjects.

#### Statistical analysis

Data were assessed for normality using the Shapiro-Wilk test. Statistical tests appropriate to distribution were performed.

For sEMG data during exercise, a linear mixed model with subject and subject × condition (BFR-E or E-only) as random factors and contraction block (1 to 9), condition, time since lesion (days) and contraction block × condition as fixed factors was performed.

For M-max and MEP data, for each time, each condition and each subject the (a) average M-wave peak-to-peak amplitude was calculated, (b) average single pulse TMS peak-to-peak amplitude was expressed as a percentage of the average M-max peak-to-peak amplitude, (c) average SICI peak-to-peak amplitude was expressed as a percentage of the average single pulse TMS peak-to-peak amplitude and, (d) average ICF peak-to-peak amplitude was expressed as a percentage of the average single pulse peak-to-peak amplitude. Linear mixed models with subject and subject × condition (BFR-E or E-only) as random factors and time (T0, T1, T2 and T3), condition, time since lesion (days) and time × condition as fixed factors were performed for (a)–(d).

For the numerical rating scale data, Wilcoxon signed ranks tests compared BFR-E and E-only data for pain, discomfort, difficulty, safety, focus and fatigue.

When appropriate, means and 95% confidence intervals or median and interquartile ranges were reported. Significance was set to $p < 0.05$.

## 3. Results

Fifteen participants were recruited for the study. One participant was excluded from the study after completing day 1. For this participant, on day 2, prior to any testing, the systolic brachial blood pressure was >160 mmHg. As per the inclusion/exclusion criteria, the patient was removed from the study and data from day 1 were discarded. A neurologist was informed about the patients' high blood pressure, and after further tests, the patient was deemed medically stable. The patient received BFR-E on day 1, seven days prior, with no complications after testing. It was deemed that the increase in blood pressure prior to day 2 was not related to the BFR-E session.

The remaining 14 participants are described in Table 1. All participants had post-exercise numerical rating scores and during exercise sEMG data for both BFR-E and E-only days. We had complete TMS and M-wave data for eight participants, complete M-wave data but no TMS data for a further five participants and no TMS and M-wave data for one participant. Four participants had no discernible MEPs at 60% of the MSO on day 1 when establishing TMS thresholds and were not tested further using TMS. One participant had discernible MEPs at 60% of the MSO on day 1 but not on day 2, and all TMS data for this participant were removed. One participant felt uncomfortable with electrical stimulation and TMS, and declined to have TMS and peripheral electrical stimulation.

### *3.1 Muscle activity during training*

Fig. 2 shows example rectified and smoothed data for one participant during exercise in BFR-E and E-only conditions.

During exercise there was a significant main effect of contraction-block ($p < 0.05$) but no condition × contraction block interaction ($p = 0.149$) and no main effect of condi-

tion ($p$ = 0.364) or time since stroke ($p$ = 0.402). Table 2 shows the modelled estimates of fixed effects of condition and contraction block. Pairwise comparisons for each contraction block minus contraction block 1 and condition are shown in Table 3.

### *3.2 Neurophysiological measures*

Fig. 3 shows example raw data for one participant for M-max, single pulse TMS, SICI and ICF stimulation paradigms before and after BFR-E and E-only conditions.

There was no significant condition × time interaction for M-max amplitude ($p$ = 0.463), single pulse TMS amplitude ($p$ = 0.343), SICI amplitude ($p$ = 0.973) or ICF amplitude ($p$ = 0.850). Table 4 shows the modelled estimates of fixed effects of condition and time. There was no main effect of time for M-max amplitude ($p$ = 0.136), single pulse TMS amplitude ($p$ = 0.157), SICI amplitude ($p$ = 0.797) or ICF amplitude ($p$ = 0.354). There was significant main effect of condition for ICF amplitude ($p$ = 0.009) but not M-max amplitude ($p$ = 0.329), single pulse TMS amplitude ($p$ = 0.521) or SICI amplitude ($p$ = 0.698). There was no significant main effect of time since lesion for M-max amplitude ($p$ = 0.671), single pulse TMS amplitude ($p$ = 0.996), SICI amplitude ($p$ = 0.822) or ICF amplitude ($p$ = 0.783). Table 5 shows the modelled mean differences and 95% CIs of the pairwise comparisons for the main effects of time and condition.

### *3.3 Numerical rating scores*

Table 6 summarises the numerical rating scores for BFR-E and E-only. There were no differences between conditions for patient perceived pain ($p$ = 0.10), discomfort ($p$ = 0.17), fatigue ($p$ = 0.47), safety ($p$ = 0.50), focus ($p$ = 0.24) or difficulty ($p$ = 0.16).

## 4. Discussion

One session of dorsiflexion resistance exercise has not previously been compared between BFR-E and E-only conditions in participants following stroke. We found no contraction-block × condition interaction for EMG amplitude during exercise or time × condition interaction for M-max, MEP amplitude (from single pulse TMS), SICI and ICF after exercise (primary aim). There was also no difference in patient perceptions of pain, discomfort, fatigue, safety, focus or difficulty during exercise between conditions (secondary aim).

### *4.1 Neurophysiological measurements*

There were no interaction effects for single pulse stimulation, SICI and ICF. Although a main effect of condition was reported for ICF, this is a reflection of the higher ICF at baseline. Unfortunately, we could only find rMT in eight participants. For five participants the rMT could not be found on both days. Following stroke, it is common for patients to have reduced cortical excitability in the affected hemisphere compared to the unaffected hemisphere and compared to healthy controls [49]. A systematic review demonstrated large standardised main differences (SMD) and relatively narrow 95% confidence intervals (95% CI) when comparing the affected hemisphere with the unaffected hemisphere for rMT (SMD: 1.03, 95% CI: 0.84 to 1.23) and MEP amplitude (SMD: –0.96, 95% CI: –1.17 to –0.74) and the affected hemisphere with healthy controls for rMT (SMD: 1.24, 95% CI: 0.81 to 1.67) and MEP amplitude (SMD: –0.64, 95% CI: –0.93 to 0.34) [49]. These differences were apparent in both early and chronic phases of stroke [49]. Given this, the inability to determine a rMT in five participants, may not be unexpected.

When determining our target sample size of 16, we expected that although rMT may be higher and MEP amplitude maybe reduced in our cohort, we would still be able to attain a rMT. It is difficult to ascertain why our cohort had so many non-responders when patients were relatively well functioning and had a dorsiflexor MMT strength of >3. Non-responders to TMS have been reported by other investigators but not all. Huynh *et al*. [50] performed TMS to the ipsilesional cortex to the contralateral Abductor Pollicis Brevis and found that 6/31 stroke participants had no MEPs, 6 days after the lesion onset. Further, Stinear *et al*. [61] used TMS to assess the ipsilesional cortex to the ipsilateral Extensor Carpi Radialis and found that 9/40 patients had small or absent MEPs, 2 weeks after the lesion onset. Although reported in the above-mentioned studies, other studies adjust estimates for non-responders [62] or may not report on non-responders at all [63]. If this is the case, it is possible that the number of patients that were unresponsive to TMS in our study is actually representative of people that have a minimally responsive/unresponsive ipsilesional cortex when attempting to stimulate the contralateral tibialis anterior following stroke. Dharmadasa *et al*. [64] postulated that inexcitability may determine a poorer clinical profile in patients with amyotrophic lateral sclerosis as postulated in upper extremity rehabilitation following stroke [61]. Given this, the inexcitability observed in the tibialis anterior may be related to a clinical profile, associated with recovery. Although possible, our study does not have sufficient participant number or sufficient follow up time points to further explore this hypothesis.

A further consideration is that the responses from patients in our study may have been too variable to observe a consistent effect. The patients differed in the time since stroke, location of stroke and type of stroke, which can increase inter-subject variability of neurophysiological responses [46]. In our analysis, we adjusted for time since lesion (as a continuous variable) and found no effect for any neurophysiological measure. We did not add location of stroke or stroke severity as a factor as we did not have sufficient patient numbers with each to do this however a cross over design was chosen to reduce some of this variance.

**Table 1. Characteristics of included patients.**

| Patient ID | Age | Sex | Time since lesion (days) | Type of stroke | Lesion location | Aff leg | Sys-BP (mmHg) | Dia-BP (mmHg) | Height (cm) | Mass (kg) | 10MWT (s) | MAS PFs/DFs | MMT PFn/DFn | TMS/Estim |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 57 | F | 28 | I | MCA | R | 142 | 90 | 169 | 67 | 11.4 | 1+/0 | 5/4 | –/+ |
| 2 | 65 | F | 540 | I | MCA | R | 124 | 68 | 168 | 83 | 9.14 | 3/0 | 5/4 | –/+ |
| 3 | 58 | F | 25 | I | Pons | L | 120 | 74 | 160 | 76 | 7.85 | 2/0 | 5/5 | –/+ |
| 4 | 79 | M | 293 | H | MCA, Th | R | 133 | 63 | 178 | 80 | 19.95 | 2/0 | 4+/4+ | +/+ |
| 5 | 65 | M | 206 | I | MCA | R | 150 | 90 | 171 | 83 | 12.73 | 1/0 | 4+/4 | +/+ |
| 6 | 62 | F | 123 | H | F-lobe | R | 118 | 88 | 178 | 87 | 9.88 | 0/1 | 4+/4+ | +/+ |
| 7 | 59 | F | 113 | I | BG | L | 128 | 63 | 172 | 65 | 12.21 | 1+/0 | 5/4+ | +/+ |
| 8 | 64 | M | 430 | I | IC | R | 140 | 88 | 173 | 85 | 11.64 | 1+/0 | 5/4+ | –/+ |
| 9 | 55 | F | 66 | I | MCA | R | 124 | 74 | 164 | 93 | 23.75 | 1+/0 | 4/3+ | –/– |
| 10 | 36 | F | 400 | I | BG | R | 118 | 90 | 169 | 87 | 9.87 | 3/0 | 4+/4 | +/+ |
| 11 | 57 | M | 418 | I | BG | R | 124 | 66 | 180 | 90 | 10.44 | 1+/0 | 4+/5 | –/+ |
| 12 | 52 | M | 196 | I | BG, Pons | R | 126 | 84 | 183 | 95 | 9.21 | 2/0 | 5/4+ | +/+ |
| 13 | 47 | M | 118 | I | MCA | L | 124 | 74 | 183 | 99 | 6.63 | 1+/0 | 5/5 | +/+ |
| 14 | 62 | M | 431 | I | Th | R | 120 | 80 | 172 | 76 | 13.38 | 1+/0 | 5/4+ | +/+ |

F, Female; M, Male; I, ischemic; H, haemorrhagic; R, Right; L, Left; MCA, Middle Cerebral Artery; Th, Thalamus; F-lobe, Frontal lobe; BG, Basal Ganglia; IC, Internal Capsule; Sys-BP, Systolic blood pressure; Dia-BP, Disatolic blood pressure; 10MWT, 10 meter walk test time; MAS, Modified Ashworth Scale; MMT, Manual muscle Test; PFs, Plantarflexors; DFs, Dorsiflexors; PFn, Platarflexion; DFn, Dorsiflexion; TMS, Transcranial Magnetic Stimulation; Estim, Peripheral Electrical Stimulation; '+', performed; '–', not performed.

**Table 2. Modelled estimates (95% CIs) of the fixed effects for condition and contraction block (n = 14).**

| | | Contraction block (estimate (95% CI)) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Condition | C1 | C2 | C3 | C4 | C5 | C6 | C7 | C8 | C9 |
| Contraction amplitude, RMS | BFR-E | 116 (91 to 141) | 107 (82 to 132) | 104 (79 to 129) | 105 (80 to 130) | 103 (78 to 128) | 103 (78 to 128) | 113 (88 to 138) | 106 (81 to 131) | 107 (82 to 132) |
| | E-only | 111 (86 to 136) | 101 (76 to 126) | 98 (73 to 123) | 94 (69 to 119) | 94 (69 to 119) | 93 (68 to 118) | 106 (81 to 131) | 93 (68 to 118) | 91 (66 to 116) |

**Table 3. Modelled mean differences (95% CIs) of the pairwise comparisons for the main effects of contraction block and condition (n = 14).**

| | Main effect (contraction block) (minus C1) | | | | | | | | Main effect (condition) |
|---|---|---|---|---|---|---|---|---|---|
| | C2 | C3 | C4 | C5 | C6 | C7 | C8 | C9 | BFR-E minus E-only |
| | mean difference (95% CI) | mean difference (95% CI) | mean difference (95% CI) | mean difference (95% CI) | mean difference (95% CI) | mean difference (95% CI) | mean difference (95% CI) | mean difference (95% CI) | mean difference (95% CI) |
| Contraction amplitude, RMS | –9 (–13 to –5)* | –12 (–16 to –8)* | –14 (–18 to –10)* | –15 (–19 to –11)* | –15 (–19 to –11)* | –4 (–8 to 0)* | –14 (–18 to –10)* | –15 (–19 to –11)* | 9 (–11 to 29) |

* represents significant differences to $p < 0.05$; C, contraction block; RMS, root mean squared; All values are rounded to whole numbers.

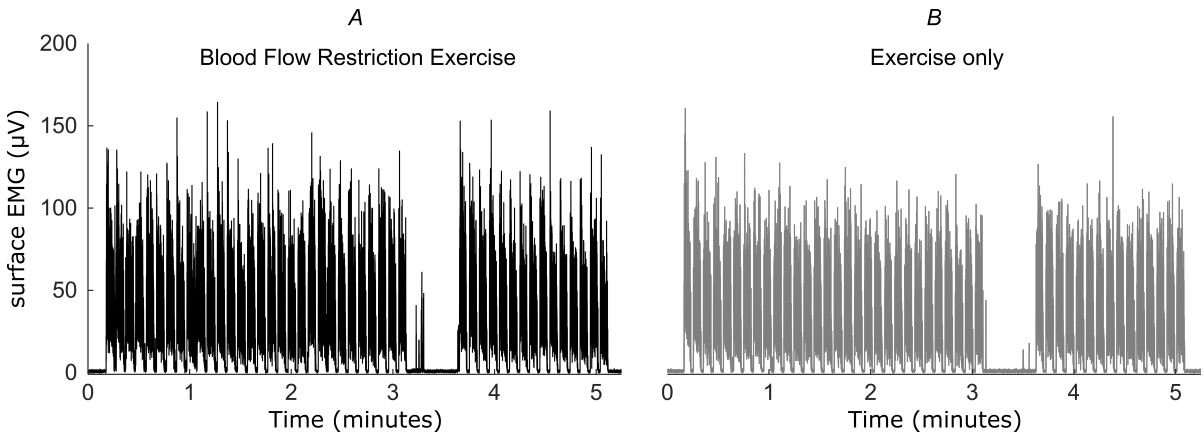


**Fig. 2. Example traces of the rectified and smoothed (20 Hz low pass Butterworth filter) surface EMG ($\mu$V) of the 45 contractions for a representative subject during Blood Flow Restriction Exercise (A, black lines) and Exercise only (B, grey lines) conditions.**

Taken together, although we almost attained our target of 16 participants, due to the number of non-responders and response variability, our study was likely underpowered to determine changes/differences in TMS measurements if a difference exists. While we acknowledge that this is a significant limitation, non-publication of non-significant results, and 'file-drawer' publications, has been highlighted as a significant problem in TMS research [65]. As such, we decided to disseminate our results rather than not disseminate the results at all.

Although potentially underpowered, it is also possible that there is little difference in TMS measurements with exercise (without BFR). Although E-only paradigms in healthy subjects have shown SICI disinhibition [66–68], some have not [69]. Further, in people with chronic stroke SICI in the abductor pollicis brevis was not different for all time points after training following a single 15 min bout of repetitive thumb abduction training [55]. Our exercise protocol was shorter compared to these paradigms and perhaps too short to induce changes in SICI. Further, our paradigm was in lower limb muscles which can alter projections to muscles [70]. Similarly to SICI, there was no significant interaction in ICF between time and BFR-E and E-only conditions. Although previous studies have shown changes in ICF following exercise in healthy people [39,68,69] and stroke patients [55], not all have in E-only [39] or BFR-E [39] conditions. The result of our study could mean that SICI and ICF in people with stroke are not different when comparing BFR-E and E-only. Alternatively, the lack of difference between the BFR-E and E-only could be that the exercise intensity was too low to result in sufficient fatigue in the BFR-E condition and/or occlusion pressures used were too low to influence SICI. Studies that have demonstrated altered SICI as a result of BFR-E, have used significantly higher pressures for longer periods of time (>200 mmHg) [71]. Such protocols however, would contribute to more discomfort and pain; potentially reducing the tolerability of BFR-E [58].

*4.2 Numerical rating scores*

Safety and comfort are important aspects when assessing feasibility of new rehabilitation strategies before designing larger studies to test its effectiveness [72]. In our study, patients felt safe during both interventions with no difference between interventions. In addition, subjects reported minimal discomfort with no reported or observed adverse reactions. Although this is encouraging, based on our findings we do not believe that BFR-E should be used in all people with stroke, in all settings. Participants were selected based on a stringent inclusion and exclusion criteria and may not represent all people following stroke. In this study, exercise was overseen by a physiotherapist in an inpatient hospital with a neurologist on standby and a local medical emergency response team in case of emergency, which does not reflect all clinical settings. In our sample, participants perceived exercise as minimally fatiguing. However, in stroke populations with different inclusion/exclusion criteria, with more fatiguing exercises over more sessions, it is possible that adverse reactions are more likely to occur. Previous research has shown that the frequency of self-reported fatigue affects 69.5% of people 1-year following stroke [73] and is 68% more prominent in people with stroke than healthy people [74]. If similar studies are performed in the future, we recommend that this is considered when choosing exercise intensity and training setting.

Patients reported minimal pain and discomfort and no difference in pain and discomfort between BFR-E and E-only conditions. This is encouraging as people with stroke are more likely to comply with exercise that doesn't cause pain or discomfort [75]. However, it also highlights that exercise was (perhaps) too easy or that cuff pressures were too low for most patients as some pain/discomfort is expected during BFR-E [58]. Future studies should consider increasing exercise intensity and cuff pressures during BFR-E to potentially increase the effects of BFR-E.

**Table 4. Modelled estimates (95% CIs) of the fixed effects for condition and time (n = 8).**

| Variable | Condition | T0 — estimate (95% CI) | T1 — estimate (95% CI) | T2 — estimate (95% CI) | T3 — estimate (95% CI) |
|---|---|---|---|---|---|
| M-max amplitude, µV | BFR-E | 2307 (1877 to 2737) | 2129 (1699 to 2559) | 2184 (1754 to 2614) | 2234 (1804 to 2664) |
| | E-only | 2384 (1954 to 2814) | 2366 (1936 to 2796) | 2307 (1877 to 2727) | 2419 (1989 to 2849) |
| Single pulse amplitude, % of M-max | BFR-E | 20 (13 to 27) | 20 (13 to 27) | 21 (14 to 28) | 20 (13 to 27) |
| | E-only | 19 (12 to 26) | 20 (13 to 27) | 22 (15 to 29) | 25 (18 to 32) |
| SICI amplitude, % of single pulse amplitude | BFR-E | 74 (59 to 89) | 74 (60 to 89) | 76 (61 to 91) | 71 (57 to 86) |
| | E-only | 74 (59 to 89) | 74 (59 to 89) | 80 (65 to 94) | 74 (59 to 89) |
| ICF amplitude, % of single pulse amplitude | BFR-E | 188 (81 to 295) | 187 (80 to 294) | 164 (57 to 270) | 161 (55 to 268) |
| | E-only | 305 (198 to 412) | 296 (189 to 403) | 224 (117 to 331) | 255 (149 to 362) |

All values are rounded to whole numbers; T0 = pre-exercise; T1 = immediately post-exercise, T2 = 10 min post-exercise; T3 = 20 min post-exercise.

**Table 5. Modelled mean differences (95% CIs) of the pairwise comparisons for the main effects of time and condition, for peripheral electrical stimulation (M-max-amplitude) (n = 13) and TMS measurements (Single pulse, SICI and ICF —amplitude) (n = 8).**

| Variable | Main effect (time) | | | Main effect (condition) |
|---|---|---|---|---|
| | T1 minus T0 | T2 minus T0 | T3 minus T0 | BFR-E minus E-only |
| | mean difference (95% CI) | mean difference (95% CI) | mean difference (95% CI) | mean difference (95% CI) |
| M-max amplitude, µV | –98 (–205 to 9) | –100 (–207 to 7) | –19 (–126 to 87) | –156 (–470 to 159) |
| Single pulse amplitude, % of M-max | 1 (–2 to 4) | 2 (–1 to 6) | 4 (0 to 7) | –1 (–5 to 3) |
| SICI amplitude, % of single pulse amplitude | 0 (–10 to 11) | 4 (–6 to 14) | –1 (–11 to 9) | –2 (–10 to 7) |
| ICF amplitude, % of single pulse amplitude | –5 (–74 to 64) | –53 (–121 to 16) | –38 (–107 to 31) | –95* (–165 to –25) |

All values are rounded to whole numbers; * represents significant differences to $p < 0.05$; T0 = pre-exercise; T1 = immediately post-exercise, T2 = 10 min post-exercise; T3 = 20 min post-exercise.

**Table 6. Median (IQR) BFR-E and E-only in the numeric rating scores (0–10) for pain, discomfort, fatigue, satisfaction, focus and difficulty (n = 14).**

| | BFR-E | E-only |
|---|---|---|
| | median (IQR) | median (IQR) |
| Pain | 0 (0–1) | 0 (0–0) |
| Discomfort | 0 (0–1) | 0 (0–1) |
| Fatigue | 3 (1–4) | 2 (1–4) |
| Safety | 10 (10–10) | 10 (9–10) |
| Focus | 10 (8–10) | 10 (9–10) |
| Difficulty | 1 (0–6) | 1 (0–3) |

Numerical rating scores rounded to whole numbers.

### *4.3 Limitations*

In this study, participants generally had few comorbidities and high mobility (i.e., could walk 10 meters with or without walking aids), which is not representative of many people following stroke who are weaker and/or lower functioning. Although the participants included in our study were relatively well-functioning, as we included a convenience-based sample, there was some heterogeneity in the included population. For example, some patients received thrombolysis on admission to acute care (subject 10 and 11 received thrombolysis, subject 8 was missing and the remaining did not receive thrombolysis) and some had depression (subject 3, 8 and 14). Unfortunately, we were not able to attain the medication status, did not measure/attain general post-stroke fatigue nor have reliable/valid data on thrombectomy. These are factors that can influence neural recovery and peripheral responses to TMS. Furthermore, although all patients included in the study had deficits as a result of the stroke (as this was one of our questions in the initial interview), we cannot definitively rule out that some of the participants may have had existing issues which further exacerbated the impairment caused by the stroke. It would have been ideal to have medication status, post stroke fatigue, thrombectomy data and pre-existing deficits. However, as we used a cross-over type design and accounted for this in our analysis, although a limitation, it is part of the difficulties when conducting research in an inpatient setting and using a convenience based sample. Exercise was performed in an inpatient hospital with significant safety measures in place, should a patient experience distress. Future research using similar paradigms must account for this to ensure safety of patients when performing BFR-E. Furthermore, our training protocol was short, over 1 session, and does not account for the amount of practice required for functional recovery after stroke nor the reality of most clinical settings.

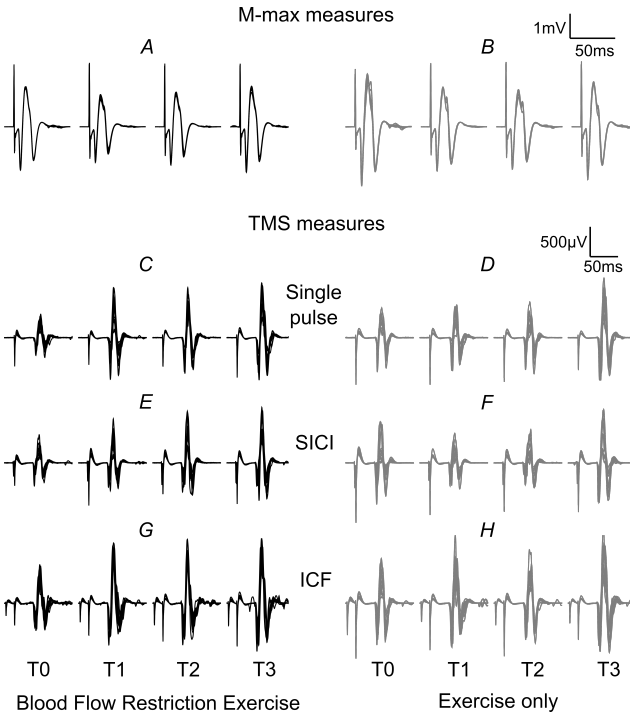


**Fig. 3. Example traces of raw surface EMG ($\mu$V) data for a representative subject for Blood Flow Restriction Exercise (black lines) and Exercise only (grey lines) conditions.** Data are shown for pre-exercise (T0), immediately post-exercise (T1), 10 min post-exercise (T2) and 20 min post-exercise (T3). (A,B) Surface EMG traces of the tibialis anterior following stimulation of the common peroneal nerve at 1.5 × the maximal stimulation intensity to elicit M-max for 10 stimuli at each timepoint. (C,D) Surface EMG traces of the tibialis anterior following single pulse TMS stimulated at 120% of the motor threshold for 12 stimuli at each timepoint. (E–H) Surface EMG traces of the tibialis anterior following paired pulse TMS with the first pulse delivered at 80% of the resting motor threshold and the second pulse delivered at 120% of the resting motor threshold with interstimulus intervals of 2 ms (E and F, SICI) and 15 ms (G and H, ICF) for 12 stimuli at each timepoint for each stimulus type.

## 5. Conclusions

To our knowledge, this is the first study to specifically train the ankle dorsiflexors in stroke patients using BFR-E. Although 14 participants completed the study protocol, only eight participants completed TMS measures on both days. Post exercise SICI, ICF and single pulse TMS showed no interaction effect for conditions × time. The lack of interaction effects may have been due to an underpowered experimental design. Participants reported minimal fatigue and discomfort in both conditions, which although may increase patient compliance to the exercise regime, may also indicate that the occlusion pressure and exercise intensity was too low. Although we can conclude that a single session of BFR-E was safe, feasible and well tolerated, our results are not generalizable to lower functioning people with stroke. Further studies investigating different (more intense) exercise protocols and/or longer term training (e.g., over weeks or months) are welcomed to clarify the effects of BFR-E.

## Abbreviations

SICI, Short interval intracortical inhibition; ICF, Intracortical Facilitation; MEP, Motor Evoked Potential; BFR-E, Exercise with Blood Flow Restriction; E-only, Exercise without Blood Flow Restriction; EMG, Electromyographic activity; rMT, resting Motor Threshold; MSO, Maximal Stimulator Output.

## Author contributions

Conceptualization—ETNS, JFN, PWS; Project Administration—SSK, PWS; Methodology—SSK, ETNS, JFN, PWS; Resources—ETNS, JFN; Investigation—ETNS, SSK, PWS; Formal Analysis—PWS; Interpretation of data—SSK, ETNS, ML, CQdO, JFN, PWS; Visualization—PWS; Writing—Original Draft Preparation—SSK, ETNS, ML, CQdO, JFN, PWS; Writing—Review & Editing—SSK, ETNS, ML, CQdO, JFN, PWS.

## Ethics approval and consent to participate

The study conformed to the Declaration of Helsinki and was approved by the local scientific ethics committee (approval number: 1-10-72-279-14) and the Danish Data Protection agency (approval number: 1-16-02-520-14). Participants were recruited via an inpatient rehabilitation ward or had provided details in previous studies allowing researchers to contact them for future studies. All subjects provided written informed consent prior to undertaking the study.

## Acknowledgment

We would like to thank the participants for being part of this study.

## Funding

This study was supported by a grant (project nr. 614864) from the Health Research Fund of the Central Denmark Region to Peter Stubbs.

## Conflict of interest

The authors declare no conflict of interest.

## References

[1] Pollock A, Baer G, Campbell P, Choo PL, Forster A, Morris J, *et al.* Physical rehabilitation approaches for the recovery of function and mobility following stroke. Cochrane Database of Systematic Reviews. 2014; 2014: CD001920.

[2] Lexell J, Flansbjer UB. Muscle strength training, gait perfor-

mance and physiotherapy after stroke. Minerva Medica. 2008; 99: 353–368.
[3] Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. Lancet. 2011; 377: 1693–1702.
[4] Studenski SA, Wallace D, Duncan PW, Rymer M, Lai SM. Predicting stroke recovery: Three and six-Month rates of patient-centered functional outcomes based on the Orpington Prognostic Scale. Journal of the American Geriatric Society. 2001; 49: 308–312.
[5] Patterson SD, Hughes L, Head P, Warmington S, Brandner C. Blood flow restriction training: A novel approach to augment clinical rehabilitation: How to do it. British Journal of Sports Medicine. 2017; 51: 1648–1649.
[6] Scott B, Slattery K, Sculley D, Dascombe B. Hypoxia and Resistance Exercise: A Comparison of Localized and Systemic Methods. Sports Medicine. 2014; 44: 1037–1054.
[7] Abbott N, Patabendige A, Dolman D, Yusof S, Begley D. Structure and function of the blood-brain barrier. Neurobiology of Disease. 2010; 37: 13–25.
[8] Magladery J, McDougal D, Stoll J. Electrophysiological studies of nerve and reflex activity in normal man. II. The effects of peripheral ischemia. Bulletin of the Johns Hopkins Hospital. 1950; 86: 291–312.
[9] Baker BS, Stannard MS, Duren DL, Cook JL, Stannard JP. Does blood flow restriction therapy in patients older than age 50 result in muscle hypertrophy, increased strength, or greater physical function? A systematic review. Clinical Orthopaedics and Related Research. 2020; 478: 593–606.
[10] Cook SB, LaRoche DP, Villa MR, Barile H, Manini TM. Blood flow restricted resistance training in older adults at risk of mobility limitations. Experimental Gerontology. 2017; 99: 138–145.
[11] Vechin FC, Libardi CA, Conceição MS, Damas FR, Lixandrão ME, Berton RPB, *et al.* Comparisons between low-intensity resistance training with blood flow restriction and high-intensity resistance training on quadriceps muscle mass and strength in elderly. Journal of Strength and Conditioning Research. 2015; 29: 1071–1076.
[12] Clarkson MJ, May AK, Warmington SA. Chronic blood flow restriction exercise improves objective physical function: A systematic review. Frontiers in Physiology. 2019; 10: 1–12.
[13] Hughes L, Patterson SD, Haddad F, Rosenblatt B, Gissane C, McCarthy D, *et al.* Examination of the comfort and pain experienced with blood flow restriction training during post-surgery rehabilitation of anterior cruciate ligament reconstruction patients: A UK National Health Service trial. Physical Therapy in Sport. 2019;39: 90–98.
[14] Hughes L, Rosenblatt B, Haddad F, Gissane C, McCarthy D, Clarke T, *et al.* Comparing the effectiveness of blood flow restriction and traditional heavy load resistance training in the post-surgery rehabilitation of Anterior Cruciate Ligament reconstruction patients: A UK National Health Service randomised controlled trial. Sport Medicine. 2019; 49: 1787–1805.
[15] Li S, Shaharudin S, Abdul Kadir MR. Effects of blood flow restriction training on muscle strength and pain in patients with knee injuries: A meta-analysis. Am Journal of Physical Medicine and Rehabilitation. 2021; 100: 337–344.
[16] Ladlow P, Coppack RJ, Dharm-Datta S, Conway D, Sellon E, Patterson SD, *et al.* Low-load resistance training with blood flow restriction improves clinical outcomes in musculoskeletal rehabilitation: A single-blind randomized controlled trial. Frontiers in Physiology. 2018; 9: 1–14.
[17] Bobes Álvarez C, Issa-Khozouz Santamaría P, Fernández-Matías R, Pecos-Martín D, Achalandabaso-Ochoa A, Fernández-Carnero S, *et al.* Comparison of blood flow restriction training versus non-occlusive training in patients with Anterior Cruciate Ligament Reconstruction or knee osteoarthritis: A systematic review. Journal of Clinical Medicine. 2020; 10: 68.
[18] Choudhary N. Arm crank ergometry with blood flow restriction technique as a feasible strategy for improving hand function in chronic stroke survivors – a randomized controlled study. International Journal of Stroke. 2020; 15: 248.
[19] Nakajima T, Kurano M, Iida H, Takano H, Oonuma H, Morita T, *et al.* Use and safety of KAATSU training:Results of a national survey. International Journal of KAATSU Training Research. 2006; 2: 5–13.
[20] Yasuda T, Meguro M, Sato Y, Nakajima T. Use and safety of KAATSU training: Results of a national survey in 2016. International Journal of KAATSU Training Research. 2017; 13: 1–9.
[21] Learmonth Y, Kistler B, Ensari I, Sandroff B, Fitschen P, Wilund K, *et al.* A novel approach to low level resistance training in multiple sclerosis; Kaatsu occlusion training. Multiple Sclerosis Journal. 2013; 19: 557.
[22] Lamberti N, Straudi S, Donadi M, Tanaka H, Basaglia N, Manfredini F. Effectiveness of blood flow-restricted slow walking on mobility in severe multiple sclerosis: A pilot randomized trial. Scandinavian Journal of Medicine & Science in Sports. 2020; 30: 1999–2009.
[23] Cohen ET, Cleffi N, Ingersoll M, Karpatkin HI. Blood-flow restriction training for a person with primary progressive Multiple Sclerosis: A case report. Physical Therapy. 2021; 101: pzaa224.
[24] Kistler B, Learmonth Y, Fitschen P, Ensari I, Biruete A, Sandroff B, *et al.* Blood-flow restriction training does not increase muscular gains in persons with Multiple Sclerosis. 2006. Medicine & Science in Sports & Exercise. 2014; 46: 551.
[25] Freitas EDS, Miller RM, Heishman AD, Aniceto RR, Larson R, Pereira HM, *et al.* The perceptual responses of individuals with multiple sclerosis to blood flow restriction versus traditional resistance exercise. Physiology & Behavior. 2021; 229: 113219.
[26] Stavres J, Singer TJ, Brochetti A, Kilbane MJ, Brose SW, McDaniel J. The Feasibility of Blood Flow Restriction Exercise in Patients With Incomplete Spinal Cord Injury. PM&R. 2018; 10: 1368–1379.
[27] Skiba G, Andrade S, Rodacki A. Effects of electro-stimulation combined with blood flow restriction affected by spinal injury muscles. Neurological Sciences. 2021. (in press)
[28] Gorgey AS, Timmons MK, Dolbow DR, Bengel J, Fugate-Laus KC, Michener LA, *et al.* Electrical stimulation and blood flow restriction increase wrist extensor cross-sectional area and flow meditated dilatation following spinal cord injury. European Journal of Applied Physiology. 2016;116: 1231–1244.
[29] Stavres J. The feasibility of blood flow restriction exercise for individuals with incomplete spinal cord injuries. Kent State University College of Education, Health, and Human Services. 2017.
[30] Krogh S, Jønsson AB, Vibjerg J, Severinsen K, Aagaard P, Kasch H. Feasibility and safety of 4 weeks of blood flow-restricted exercise in an individual with tetraplegia and known autonomic dysreflexia: a case report. Spinal Cord Series and Cases. 2020; 6: 83.
[31] Salvador AF, Schubert KR, Cruz RS de O, Corvino RB, Pereira KL, Caputo F, *et al.* Bilateral muscle strength symmetry and performance are improved following walk training with restricted blood flow in an elite paralympic sprint runner: Case study. Physical Therapy in Sport. 2016; 20: 1–6.
[32] McKay WB, Tuel SM, Sherwood AM, Stokić DS, Dimitrijević MR. Focal depression of cortical excitability induced by fatiguing muscle contraction: a transcranial magnetic stimulation study. Experimental Brain Research. 1995; 105: 276–282.
[33] Brasil-Neto JP, Pascual-Leone A, Valls-Solé J, Cammarota A, Cohen LG, Hallett M. Postexercise depression of motor evoked potentials: a measure of central nervous system fatigue. Exper-

imental Brain Research. 1993; 93: 181–184.
[34] Taylor JL, Gandevia SC. Transcranial magnetic stimulation and human muscle fatigue. Muscle & Nerve. 2001; 24: 18–29.
[35] Liepert J, Kotterba S, Tegenthoff M, Malin JP. Central fatigue assessed by transcranial magnetic stimulation. Muscle & Nerve. 1996; 19: 1429–1434.
[36] Samii A, Wassermann EM, Ikoma K, Mercuri B, Hallett M. Characterization of postexercise facilitation and depression of motor evoked potentials to transcranial magnetic stimulation. Neurology. 1996; 46: 1376–1382.
[37] Zanette G, Bonato C, Polo A, Tinazzi M, Manganotti P, Fiaschi A. Long-lasting depression of motor-evoked potentials to transcranial magnetic stimulation following exercise. Experimental Brain Research. 1995; 107: 80–86.
[38] Gandevia S. Spinal and supraspinal factors in human muscle fatigue. Physiological Reviews. 2001; 81: 1725–1789.
[39] Kjeldsen SS, Næss-Schmidt ET, Hansen GM, Nielsen JF, Stubbs PW. Neuromuscular effects of dorsiflexor training with and without blood flow restriction. Heliyon. 2019; 5: e02341.
[40] Brandner C, Warmington S, Kidgell D. Corticomotor excitability is increased following an acute bout of blood flow restriction resistance exercise. Frontiers in Human Neuroscience. 2015; 9: 652.
[41] Ilić TV, Meintzschel F, Cleff U, Ruge D, Kessler KR, Ziemann U. Short-interval paired-pulse inhibition and facilitation of human motor cortex: the dimension of stimulus intensity. Journal of Physiology. 2002; 545: 153–167
[42] Rothwell JC, Day BL, Thompson PD, Kujirai T. Short latency intracortical inhibition: one of the most popular tools in human motor neurophysiology. Journal of Physiology. 2009; 587: 11–12.
[43] Ziemann U, Lönnecker S, Steinhoff BJ, Paulus W. The effect of lorazepam on the motor cortical excitability in man. Expermintal Brain Research. 1996; 109: 127–135.
[44] Werhahn KJ, Kunesch E, Noachtar S, Benecke R, Classen J. Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. Journal of Physiology. 1999; 517: 591–597.
[45] McDonnell MN, Orekhov Y, Ziemann U. Suppression of LTP-like plasticity in human motor cortex by the GABA B receptor agonist baclofen. Experimental Brain Research. 2007; 180: 181–186.
[46] Di Lazzaro V, Pilato F, Oliviero A, Dileone M, Saturno E, Mazzone P, *et al.* Origin of Facilitation of Motor-Evoked Potentials After Paired Magnetic Stimulation: Direct Recording of Epidural Activity in Conscious Humans. Journal of Neurophysiology. 2006; 96: 1765–1771.
[47] Ni Z, Gunraj C, Chen R. Short interval intracortical inhibition and facilitation during the silent period in human. Journal of Physiology. 2007; 583: 971–982.
[48] Chen R, Tam A, Butefisch C, Corwell B, Ziemann U, Rothwell J, *et al.* Intracortical inhibition and facilitation in different representations of the human motor cortex. Journal of Neurophysiology. 1998; 80: 2870–2881.
[49] McDonnell MN, Stinear CM. TMS measures of motor cortex function after stroke: A meta-analysis. Brain Stimulation. 2017;10: 721–734.
[50] Huynh W, Vucic S, Krishnan A V., Lin CSY, Kiernan MC. Exploring the evolution of cortical excitability following acute stroke. Neurorehabilitation and Neural Repair. 2016; 30: 244–257.
[51] Liepert J, Storch P, Fritsch A, Weiller C. Motor cortex disinhibition in acute stroke. Clinical Neurophysiology. 2000; 111: 671–676.
[52] Levy LM, Ziemann U, Chen R, Cohen LG. Rapid modulation of GABA in sensorimotor cortex induced by acute deafferentation. Annals of Neurology. 2002; 52: 755–761.
[53] McNulty PA, Macefield VG, Taylor JL, Hallett M. Cortically evoked neural volleys to the human hand are increased during ischaemic block of the forearm. Journal of Physiology. 2002; 538: 279–288.
[54] Blicher JU, Near J, Næss-Schmidt E, Stagg CJ, Johansen-Berg H, Nielsen JF, *et al.* GABA levels are decreased after stroke and GABA changes during rehabilitation correlate with motor improvement. Neurorehabilitation and Neural Repair. 2015; 29: 278–286.
[55] Blicher JU, Jakobsen J, Andersen G, Nielsen JF. Cortical Excitability in Chronic Stroke and Modulation by Training: A TMS Study. Neurorehabilitation and Neural Repair. 2009; 23: 486–493.
[56] Julious SA. Sample size of 12 per group rule of thumb for a pilot study. Pharmaceutical Statistics. 2005; 4: 287–291.
[57] Cram J, Kasman G, Holtz J. Introduction to Surface Electromyography. Aspen Publication: Gaithersburg, MA. 1998.
[58] Næss-Schmidt E, Morthorst M, Pedersen AR, Nielsen JF, Stubbs PW. Corticospinal excitability changes following blood flow restriction training of the tibialis anterior: a preliminary study. Heliyon. 2017; 3: e00217.
[59] Fahs CA, Rossow LM, Loenneke JP, Thiebaud RS, Kim D, Bemben DA, *et al.* Effect of different types of lower body resistance training on arterial compliance and calf blood flow. Clinical Physiology and Functional Imaging. 2012; 32: 45–51.
[60] Brandner C, Kidgell D, Warmington S. Unilateral bicep curl hemodynamics: Low-pressure continuous vs high-pressure intermittent blood flow restriction. Scandinavian Journal of Medicine & Science in Sports. 2015; 25: 770–777.
[61] Stinear C, Barber PA, Petoe M, Anwar S, Byblow W. The PREP algorithm predicts potential for upper limb recovery after stroke. Brain. 2012; 135: 2527–2535.
[62] Bütefisch CM, Weßling M, Netz J, Seitz RJ, Hömberg V. Relationship between interhemispheric inhibition and motor cortex excitability in subacute stroke patients. Neurorehabilitation and Neural Repair. 2008; 22: 4–21.
[63] Héroux ME, Loo CK, Taylor JL, Gandevia SC. Questionable science and reproducibility in electrical brain stimulation research. PLoS ONE. 2017;12: e0175635.
[64] Dharmadasa T, Howells J, Matamala JM, Simon NG, Burke D, Vucic S, *et al.* Cortical inexcitability defines an adverse clinical profile in amyotrophic lateral sclerosis. European Journal of Neurology. 2021; 28: 90–97.
[65] Heroux ME, Taylor JL, Gandevia SC. The Use and Abuse of Transcranial Magnetic Stimulation to Modulate Corticospinal Excitability in Humans. PLoS ONE. 2015; 10: e0144151.
[66] Perez MA, Lungholt BKS, Nyborg K, Nielsen JB. Motor skill training induces changes in the excitability of the leg cortical area in healthy humans. Experimental Brain Research. 2004; 159: 197–205.
[67] Liepert J, Classen J, Cohen LG, Hallett M. Task-dependent changes of intracortical inhibition. Experimental Brain Research. 1998; 118: 421–426.
[68] Latella C, Goodwill AM, Muthalib M, Hendy AM, Major B, Nosaka K, *et al.* Effects of eccentric versus concentric contractions of the biceps brachii on intracortical inhibition and facilitation. Scandinavian Journal of Medicine & Science in Sports. 2019; 29: 369–379.
[69] Blicher JU, Nielsen JF. Cortical and spinal excitability changes after robotic gait 1raining in healthy participants. Neurorehabilitation and Neural Repair. 20082009; 23: 143–149.
[70] Petersen N, Pyndt HS, Nielsen JB. Investigating human motor control by transcranial magnetic stimulation. Experimental Brain Research.. 2003; 152: 1–16.
[71] Ziemann U, Corwell B, Cohen LG. Modulation of plasticity in

human motor cortex after forearm ischemic nerve block. Journal of Neuroscience. 1998; 18: 1115–1123.
[72] Tickle-Degnen L. Nuts and Bolts of Conducting Feasibility Studies. American Journal of Occupational Therapy. 2013; 67: 171–176.
[73] Schepers VP, Visser-Meily AM, Ketelaar M, Lindeman E. Post-stroke fatigue: Course and its relation to personal and stroke-related factors. Archives of Physical Medicine and Rehabilitation. 2006; 87: 184–188.
[74] Ingles J, Eskes G, Phillips M. Fatigue after stroke. Archives of Physical Medicine and Rehabilitation. 1999; 80: 173–178.
[75] Miller KK, Porter RE, DeBaun-Sprague E, Van Puymbroeck M, Schmid AA. Exercise after stroke: Patient adherence and beliefs after discharge from rehabilitation. Topics in Stroke Rehabilitation. 2017; 24: 142–148.