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Remote ischaemic conditioning for fatigue after stroke (RICFAST): A pilot randomised controlled trial

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ABSTRACT

Background: Post stroke fatigue (PSF) affects 50 % of stroke survivors, and can be disabling. Remote ischaemic conditioning (RIC), can preserve mitochondrial function, improve tissue perfusion and may mitigate PSF. This pilot randomised controlled trial evaluates the safety and feasibility of using RIC for PSF and evaluated measures of cellular bioenergetics.

Methods: 24 people with debilitating PSF (7 item Fatigue Severity Score, FSS-7 > 4) were randomised (1:1) in this single-centre phase 2 study to RIC (blood pressure cuff inflation around the upper arm 200 mmHg for 5 min followed by 5 min of deflation), or sham (inflation pressure 20 mmHg), repeated 4 cycles, 3 times per week for 6 weeks. Primary outcomes were safety, acceptability, and compliance. Secondary outcomes included FSS-7, 6 min walking test (6MWT), peak oxygen consumption (VO_2peak), ventilatory anaerobic threshold (VAT), and muscle adenosine triphosphate (ATP) content measured using 31-phosphorous magnetic resonance spectroscopy of tibialis anterior.

Results: RIC was safe (no serious adverse events, adverse events mild) and adherence excellent (91 % sessions completed). Exploratory analysis revealed lower FSS-7 scores in the RIC group compared to sham at 6 weeks (between group difference FSS-7 -0.7, 95 %CI -2.0 to 0.6), 3 months (-1.0, 95 %CI -2.2 to 0.2) and 6 months (-0.9, 95 %CI -2.0 to 0.2). There were trends towards increased VAT, increased muscle ATP content and improved 6MWT in the RIC group.

Discussion: RIC is safe and acceptable for people with PSF and may result in clinically meaningful improvements in fatigue and muscle bioenergetics that require further investigation in larger studies.

Introduction

Stroke is a leading cause of adult death and disability affecting over 12 million new people each year worldwide,[1] imparting global economic costs of over US$700 billion.[2] Increasing stroke incidence and effective treatments improving mortality result in larger numbers of people living with longer term complications after stroke. Post-stroke fatigue (PSF) is a multi-dimensional motor-perceptive, emotional and cognitive experience characterised by exhaustion persisting even after rest.[3] It affects over 50 % of stroke survivors at some point in their recovery,[4] impairs concentration and engagement in rehabilitation, is associated with greater risk of death and dependency,[5] and poorer

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quality of life.[6] Postulated mechanisms include reduced cortical excitability,[7] elevated inflammation,[8] physical deconditioning,[9] and impaired cellular bioenergetics.[10] Evidenced-based therapies for PSF are lacking, and thus patients, carers and healthcare professionals have highlighted this problem as a major research priority.[11]

Remote ischaemic conditioning (RIC) is a strategy whereby brief, reversible episodes of ischaemia and reperfusion are delivered to a limb by cyclical application of a blood pressure (BP) cuff inflated above systolic pressures.[12] This avoids causing direct tissue injury while triggering humoral, immune, and neurogenic pathways in the body that may lead to improvements in cerebral[13] and peripheral blood flow,[14] and mitochondrial function.[15] While neuroprotective effects are being investigated widely in stroke,[16] RIC has never been studied as a treatment for fatigue, despite mechanistic effects that may render it a beneficial therapy.

This pilot study aimed to assess the safety and feasibility of RIC as a treatment for debilitating PSF, and investigated its effect on fatigue severity, walking distance and measures of cellular bioenergetics.

Methods

This phase 2, single-centre, single-blind, randomised controlled trial allocated patients with severe PSF to 6 weeks of either RIC or sham treatment, delivered 3 times weekly. The study was approved by the Northwest Research Ethics Committee, UK, and was registered with ClinicalTrials.org (NCT03794947).

Study population

Patients were recruited from the South Yorkshire and Humber region, UK, if they were aged $>$ 18 years and suffered debilitating fatigue (7-item Fatigue Severity Scale; FSS-7 $\geq$ 4) for at least 4 weeks following ischaemic or haemorrhagic stroke. Patients were excluded if it was less than 6 weeks following their index stroke, if they had significant peripheral vascular disease, lymphoedema, complex neuropathy, skin ulceration of the upper limb, significant obstructive sleep apnoea (Epworth score $>$15), depression (Patient Health Questionnaire-9 $>$14), co-existent conditions known to be associated with fatigue (e.g. multiple sclerosis, Parkinson's disease, myasthenia gravis, chronic fatigue syndrome, and cancer), a systolic BP greater than 180 mmHg, or significant physical dependence (modified Rankin Scale $>$4).

Randomisation

Participants were block randomised (1:1) using an online system (Sealed Envelope Ltd, 2017) to receive either RIC or sham intervention by an independent researcher. Participant randomisation was stratified by baseline modified Rankin Scale (mRS) score according to dependency (mRS 0-2 and mRS 3-4).

Intervention

A manual sphygmomanometer (SECA®) was used to perform the RIC and sham protocols. The RIC treatment involved inflating a blood pressure cuff around the participant's upper arm to 200 mmHg for 5 min and then deflating for 5 min. This cycle was repeated 4 times (one dose = 40 min), three times weekly for 6 weeks. Participants could choose which arm and whether to have the intervention delivered at a hospital research site (Royal Hallamshire Hospital, UK) or be taught to self-deliver it at home with the help of a family member or carer. Participants were given log books to record symptoms and side effects of treatment as well as compliance. People self-delivering RIC at home received weekly telephone calls from researchers to enquire about adverse events and ensure log book completion. Participants in the sham intervention underwent a similar protocol of activity except that their blood pressure cuffs were inflated to 20–30 mmHg instead of 200 mmHg.

Blinding

Participants were blinded to treatment allocation throughout. Care was taken to ensure patient information described the intervention as an inflation of the cuff, without mention of the pressures that would be expected to have therapeutic effects. Those self-delivering RIC or sham at home were given instructions to inflate the cuff until the dial met the sticker applied to the pressure gauge. The researcher performing the conditioning protocols and completed baseline assessments was aware of treatment allocations, while a second researcher blinded to treatment allocation completed the face-to-face follow-up assessments.

Outcome measures

Outcome measures were collected at baseline, 6 weeks (end of intervention), 3 months and 6 months. Primary outcomes included safety, acceptability and compliance. To assess safety, any adverse events (AEs) or serious adverse events (SAE defined as: death, life-threatening, requires hospitalisation or results in persistent or significant disability, congenital anomaly or birth defect)[17] either related or unrelated to RIC were recorded. Safety was pre-defined as no SAEs related to RIC. Acceptability was measured by asking participants to rate their experience of several expected side effects during the intervention sessions on a 5-point Likert scale (1 = none, 5 = extremely severe) using symptom diaries. This included rating potential adverse events, such as level of discomfort, any skin irritation/redness, pain, weakness or pins and needles. Acceptability was pre-defined as less than a third of participants reporting moderate or greater discomfort (mean score $\geq$ 3 overall). Treatment logs were used to measure compliance, pre-defined as completing $>$ 80 % of the intended 18 sessions over the 6 weeks.

Secondary outcomes measured at 6 weeks, 3 months and 6 months included the FSS-7, Patient Health Questionnaire-9 (PHQ-9), Generalised Anxiety Disorder Assessment (GAD-7), and European Quality of Life-5 Dimensions (EQ-5D-5L).The 7-item Fatigue Severity Scale (FSS-7) is a self-reported questionnaire used to measure the severity of fatigue symptoms,[18] that is validated in stroke populations with reported minimal clinically reported differences (MCID) ranging between 0.45 – 1.2 averaged points.[19] The 6-minute walk test (6MWT) assesses functional exercise capacity in stroke,[20] and was completed at baseline and at 6 weeks only as was the Barthel Index (BI).

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) at baseline and 6 weeks measured peak oxygen consumption (VO_2peak), ventilatory anaerobic threshold (VAT), and the minute ventilation/carbon dioxide slope (VE/VCO_2). Symptom-limited exercise tests were conducted using an electronically braked upright stationary cycle ergometer (Lode, Corival) linked to MetaSoft® Studio, supervised by an exercise physiologist. Continuous heart rate (HR; Polar, H10) data was combined with BP monitoring and breath-by-breath respiratory data collected using a Hans-Rudolph facemask and gas analyser (Cortex Metalyser 3B). The gas analyser was calibrated before each test with standard gas concentrations. An unloaded exercise phase lasting 3 min allowed participants to familiarise themselves with resistance-free pedalling aiming for a cadence of 60 revolutions per minute. A ramp phase then increased workload by 10 Watt per minute. Participants cycled until volitional exhaustion, symptom development (e.g. palpitations, faintness, pallor, confusion, loss of coordination or chest pain) or they were unable to maintain cadence ($<$50 rpm).[21] The VO_2peak reflects the body's maximal capacity to generate energy through aerobic metabolism and is correlated with functional capacity in stroke.[22] During incremental exercise, oxygen uptake (VO_2) and expired carbon dioxide (VCO_2) increase linearly until oxidative metabolism can no longer sustain the required

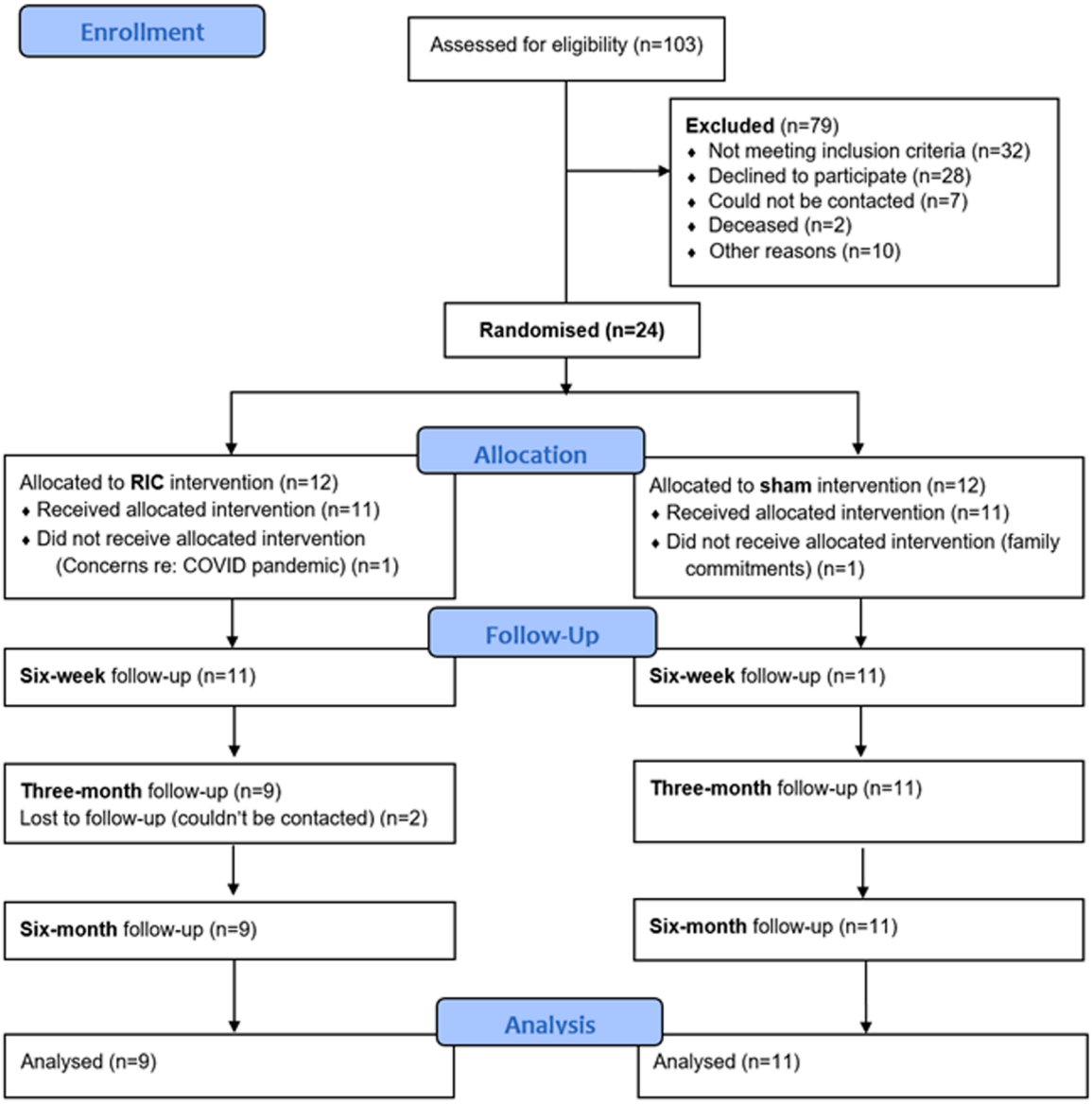

Fig. 1. Study CONSORT diagram.

workload. At this point, anaerobic metabolism is activated leading to an increase in blood lactate concentration.[23] This is termed the ventilatory anaerobic threshold (VAT), a useful measure of submaximal, sustainable exercise capacity. The V-slope method plotting VO_2 as a function of VCO_2 was used to estimate VAT.[24] The minute ventilation-to-carbon dioxide production (VE/ VCO_2) slope is an index of ventilatory efficiency and quantifies the ventilatory rate required to eliminate 1 L of CO_2,[21] and steepens (increases) in people with cardiac or pulmonary disease and with age due to reduced capacity for oxidative metabolism and increased anaerobic glycolysis.[24]

Phosphorous-31 magnetic resonance spectroscopy

Adenosine triphosphate (ATP) is hydrolysed to adenosine diphosphate (ADP) and inorganic phosphate (Pi). During sustained, effortful skeletal muscle contractions, ADP and Pi accumulate, along with hydrogen ions, contributing to skeletal muscle fatigue.[25] It is thought that RIC triggers signalling pathways that enhance mitochondrial electron transport chain function making them more resilient to states of energy (ATP) deficiency.[15] Phosphorous-31 magnetic resonance imaging (^{31}P-MRS) is a non-invasive technique that indirectly assesses tissue metabolism and mitochondrial function. ^{31}P-MRS allows quantification of skeletal muscle ATP in clinical populations.[26] In an exploratory sub-study, 8 participants with hemiparesis (4 RIC: 4 sham) underwent ^{31}P-MRS of tibialis anterior of both legs at baseline and at 6 weeks. Methodology has been described in detail previously.[27] In brief, all scans were conducted at 3 Tesla (3T) using a transmit-receive ^{31}P surface coil (Philips Healthcare, Best, Netherlands). Spectra were acquired at rest from the proximal portion of the left and right ankle dorsiflexors encompassing tibialis anterior. Placement of the top of the coil 2cm below the tibial tuberosity was cross-checked for each participant to ensure consistency. A pulse-acquire sequence was applied at rest. Spectroscopic data processing was conducted by a researcher blinded to participant group. Spectra were not apodised. Manual phasing and frequency shift of phosphocreatine to 0 ppm was checked visually in all cases to exclude distortions or spurious signals. Signal fitting of 12 resonances was undertaken using the AMARES algorithm (available with jMRUI v6.0, http://www.jmrui.eu).[28] Resulting amplitudes were corrected for T1 relaxation using published values[29] and normalised per total phosphorus signal.

Table 1
Baseline characteristics of participants. P-values reflect statistical differences between the two groups tested parametrically (ANCOVA without adjustment for randomisation as prior to randomisation) or non-parametrically (Mann-Whitney U).

Characteristic	All ($n = 24$)	RIC Intervention ($n = 12$)	Sham Intervention ($n = 12$)
Age, years (mean; SD)	58.6 (10.9)	55.5 (10.6)	61.8 (10.7)
Sex (n; %)			
Male	16 (67 %)	8 (67 %)	8 (67 %)
Female	8 (33 %)	4 (33 %)	4 (33 %)
Height, cm (mean; SD)	172.8 (7.1)	174.3 (6.7)	171.3 (7.6)
Weight, kg (mean; SD)	86.3 (19.8)	90.0 (21.3)	82.4 (18.2)
BMI (mean; SD)	29.0 (7.7)	29.9 (8.5)	28.1 (6.9)
Ethnicity (n; %)			
Caucasian	20 (84 %)	9 (75 %)	11 (92 %)
Black African	1 (4 %)	1 (8 %)	0 (0 %)
Dutch	1 (4 %)	1 (8 %)	0 (0 %)
Asian British	2 (8 %)	1 (8 %)	1 (8 %)
Index stroke type (n; %)			
Ischaemic	17 (71 %)	10 (83 %)	7 (58 %)
Haemorrhagic	7 (29 %)	2 (17 %)	5 (42 %)
Time since stroke, months (mean; SD)	39.1 (14.3)	38.5 (14.7)	39.8 (14.5)
Comorbidities (n;%)			
Prior stroke/TIA	4 (17 %)	2 (17 %)	2 (17 %)
Depression	7 (29 %)	4 (33 %)	3 (25 %)
mRS (mean; SD)	2.0 (1.1)	1.8 (0.9)	2.3 (1.2)
Baseline:			
FFS-7 (mean; SD)	5.7 (0.8)	5.8 (0.9)	5.6 (0.7)
PHQ-9 (mean; SD)	9.0 (5.0)	8.3 (4.5)	9.6 (5.7)
GAD-7 (mean; SD)	7.3 (6.8)	6.8 (6.4)	7.8 (7.5)
BI (mean; SD)	89.4 (19.6)	92.9 (13.2)	85.8 (24.5)
MOCA (mean; SD)	25.5 (3.9)	26.0 (4.4)	25.1 (3.6)
EQ5D VAS (mean; SD)	60.2 (18.4)	60.4 (19.7)	60.0 (18.0)
6MWT (m; mean; SD)	298.8 (172.8)	319.5 (166.0)	279.9 (183.9)

RIC – remote ischaemic conditioning; SD – standard deviation; BMI – body mass index; TIA – transient ischaemic attack; mRS – modified Rankin Score; FFS-7 – 7 item Fatigue Severity Scale; PHQ-9 – Patient Health Questionnaire 9; GAD-7 – Generalised Anxiety Disorder 7; BI – Barthel Index; MOCA – Montreal Cognitive Assessment; VAS – visual analogue scale; 6MWT – 6 minute walk test

Sample size and statistical analysis

Data were analysed using IBM SPSS Statistics v26. We aimed to recruit a minimum of 24 participants (12 per group) which is required to assess feasibility of an intervention and provide data to estimate the sample size for a fully powered definitive study.[30] Baseline demographic and clinical characteristics were reported descriptively as were data on safety, acceptability and compliance.

Exploratory analysis to assess between-group differences between RIC and sham for each secondary outcome measure were completed using one-way analysis of covariance (ANCOVA), using the change from baseline and adjusted for age, baseline scores and mRS (stratification variable).[31] For analysis of the FSS-7, the participant's PHQ-9 score was included as an additional covariate, due to the potential confounding effect of mood on fatigue. The adjusted mean difference and corresponding 95 % confidence intervals (CI) were reported for each outcome and timepoint.

COVID-19 pandemic factors

Study recruitment and follow up ran from October 2019 to January 2022 but was halted for 8 months during the COVID-19 pandemic. The study recommenced with strict barrier precautions, only recruiting patients vaccinated against COVID-19 who had not been affected by COVID-19 infection. As CPET was considered an aerosol-generating procedure, resumption of this outcome measure was delayed further, hence some participants were not able to have follow up CPET testing at 6 weeks. These numbers are reported.

Results

After screening 103 potentially eligible patients, 24 were recruited to the study. Two participants dropped out (1 from each group) before the 6 week follow up due to factors unrelated to the treatment (Fig. 1). A further 2 participants from the RIC group were lost to follow up prior to 3 month review. No participants developed COVID-19 infection during the intervention or follow up period up to 6 months.

Participant characteristics are detailed in Table 1. More participants had experienced haemorrhagic stroke in the sham vs RIC group (42 % vs 17 %); however the groups were otherwise well-matched. Thirteen participants (7 RIC and 6 sham) received intervention in hospital and 11 at home.

Safety, acceptability and compliance – No participants in either group experienced an SAE during the intervention period. Cutaneous petechiae at cuff site were the most common adverse effects of RIC (45 % of participants), followed by headache (27 %), dizziness (9 %), and arm swelling (9 %), numbness (9 %) and stiffness (9 %), all transitory. No sham group participants reported adverse effects. All except one participant rated the severity of these adverse events as mild; mean (SD) Likert score 1.7 (0.9) out of 5. Of the 24 participants recruited, 22 (92 %) successfully completed the 6-week intervention, 20 of whom (83 %)

Table 2
Adjusted changes in secondary outcome measures at 6 weeks, 3 months and 6 months follow up. ANCOVA models for between group differences adjusted for baseline scores, and mRS (and PHQ-9 for FSS-7).

Outcome measure	Baseline		Six-weeks			Three-months			Six-Months		
	RIC ($n = 12$) Mean; SD	Sham ($n = 12$) Mean; SD	RIC ($n = 11$) Mean; SD	Sham ($n = 11$) Mean; SD	Adjusted between-group mean difference (95 % CI)	RIC ($n = 9$) Mean; SD	Sham ($n = 11$) Mean; SD	Adjusted between-group mean difference (95 % CI)	RIC ($n = 9$) Mean; SD	Sham ($n = 11$) Mean; SD	Adjusted between-group mean difference (95 % CI)
FSS-7	5.8 (0.9)	5.6 (0.7)	3.9 (1.9)	4.7 (1.2)	-0.7 (-2.0, 0.6)	3.8 (1.3)	4.6 (1.3)	-1.0 (-2.2, 0.2)	3.5 (1.6)	4.2 (0.9)	-0.9 (-2.0, 0.2)
PHQ-9	8.3 (4.5)	9.6 (5.6)	6.5 (3.8)	7.5 (6.0)	0.6 (-3.0, 4.2)	6.6 (5.4)	4.9 (3.0)	2.4 (-1.3, 6.1)	5.8 (4.5)	7.6 (4.6)	-0.7 (-3.9, 2.2)
GAD-7	6.8 (6.4)	7.8 (7.5)	5.2 (4.0)	6.7 (5.6)	-0.5 (-2.9, 1.9)	5.1 (4.5)	5.7 (5.1)	-0.04 (-2.8, 2.7)	3.8 (4.4)	4.5 (4.1)	-0.5 (-4.2, 3.2)
EQ5D-VAS	60.4 (19.7)	60.0 (18.0)	68.4 (20.4)	67.9 (16.8)	-3.1 (-17.0, 10.8)	66.2 (22.3)	60.0 (20.7)	6.7 (-15.7, 29.0)	71.7 (15.4)	61.4 (21.8)	6.4 (-8.5, 21.2)
BI	92.9 (13.2)	85.8 (24.5)	93.6 (16.3)	88.6 (23.6)	-0.7 (-4.5, 3.1)	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*

RIC – remote ischaemic conditioning; SD – standard deviation; 95 % CI – 95 % confidence interval; FFS-7 – 7 item Fatigue Severity Scale; PHQ-9 – Patient Health Questionnaire 9; GAD-7 – Generalised Anxiety Disorder 7; BI – Barthel Index; VAS – visual analogue scale; N/A – not applicable

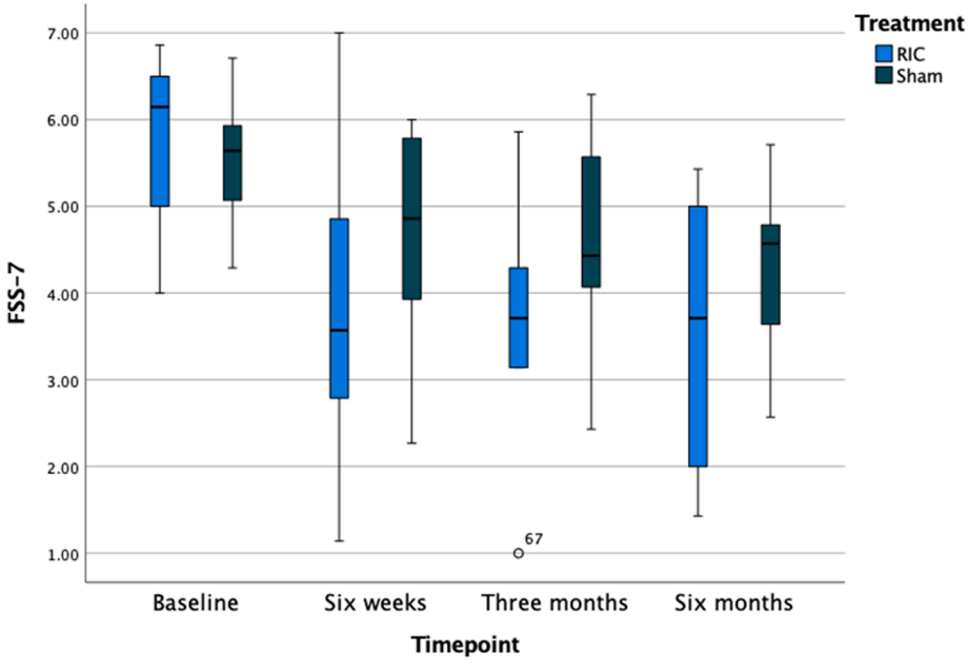

Fig. 2. Adjusted changes in mean fatigue scores (FSS-7) in RIC and sham groups at baseline, 6 weeks, 3 months and 6 months. *FFS-7 – 7 item Fatigue Severity Scale.*

Table 3
Adjusted changes in 6MWT, VO_2peak, VAT and VE/VCO_2 from baseline for both groups at 6 weeks (ANCOVA).

Outcome measure	Adjusted change from baseline to 6 weeks (mean and 95 % CI)	
	RIC	Sham
6MWT (m)	28.76 (-5.28 to 62.80)	-15.04 (-50.95 to 20.86)
VO_2peak (ml/kg/min)	0.48 (-2.11 to 3.07)	0.71 (-2.04 to 3.46)
VAT (mL/O2/kg^{-1}min^{-1})	0.21 (-1.36 to 1.79)	-0.08 (-1.75 to 1.59)
VE/VCO_2	-1.00 (-3.09 to 1.09)	1.91 (-0.31 to 4.13)

RIC – remote ischaemic conditioning; 95 % CI – 95 % confidence interval; 6MWT – 6 minute walk test; VO_2peak – peak oxygen consumption; VAT – ventilatory anaerobic threshold; VE/VCO_2 – minute ventilation to carbon dioxide ratio.

completed 100 % of intended RIC/sham cycles (18 complete 40 min sessions over the 6-week period).

Mean (SD) FSS-7 in all participants at baseline was 5.7 (0.8), with no difference between groups. Fatigue scores improved in both groups over the course of the study, however, participants in the RIC group appeared to experience greater reductions in mean FSS-7 compared to sham at 6 weeks (adjusted between group difference FSS-7 -0.7, 95 %CI -2.0 to 0.6), although this was not statistically significant (Table 2). Improvements in FSS-7 appeared to maintain at 3 and 6 months (Fig. 2), irrespective of delivery method (mean (SD) reduction FSS-7 hospital delivery -2.1 (1.1) vs home delivery -2.3 (2.1)). No clear trends were seen for PHQ-9, GAD-7, BI or EQ5D-VAS. 6MWT distances improved in the RIC group (+28.7m; 95 % CI -5.3 to 62.8) but fell in the sham group (-15.0m; 95 % CI -51.0 to 20.9) resulting in a non-significant between group mean (95 %CI) difference of 43.8m (-6.0 to 93.6).

Seventeen participants (9 RIC, 8 sham) completed CPET. CPET was not completed due to COVID-19 restrictions ($n = 3$), drop-outs ($n = 2$) and spasticity related impairments precluding completion of testing on the cycle ergometer ($n = 2$). Although participants in the RIC group exhibited numerical increases in VAT and reductions in VE/ VCO_2 slope

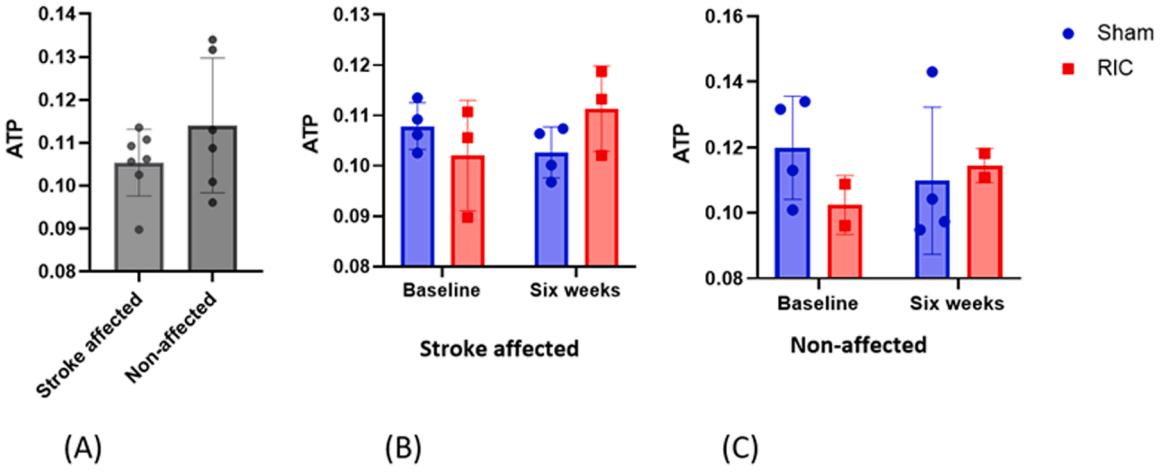

Fig. 3. 31P-MRS data showing ATP content in the tibialis anterior (A) at baseline in both affected and non-affected legs, (B) at baseline and at 6 weeks in RIC and sham groups in the stroke affected side, and (C) at baseline and at 6 weeks in RIC and sham groups in the non-affected side. *31P-MRS – Phosphorous-31 Magnetic Resonance Spectroscopy; ATP – adenosine triphosphate.*

at 6 weeks, with an inverse pattern seen in the sham group, there were no statistically significant between-group differences over time (Table 3).

Seven participants (RIC 3: sham 4) completed ^{31}P-MRS imaging of the legs at baseline and follow up ($n = 1$ drop out due to COVID-19 pandemic concerns). Amongst all participants, baseline scans demonstrated numerically higher ATP concentrations in non-affected limbs compared to stroke-affected limbs (Fig. 3, panel A). All 4 participants in the sham group experienced reductions in ATP content of the stroke-affected tibialis anterior at 6 weeks while all 3 participants in the RIC group experienced increases in ATP content (Fig. 3, panel B). No clear longitudinal effect was observed in the non-affected limbs (Figure, panel C).

Discussion

In this pilot study, delivery of RIC either at hospital or at home three times weekly for 6 weeks was safe, acceptable and feasible. Although not previously tested in PSF, our RIC safety results are consistent with previous studies in acute[32] and chronic[13] phases of stroke. The lack of any SAEs related to the intervention was reassuring, particularly as half the participants completed the treatment at home. Adverse events were common, but mild and did not seem to deter participants from completing the intervention, evident from high compliance rates. Many studies investigating RIC in the chronic phase of stroke have used automated devices,[33] however Kate et al have shown that RIC delivery using a manual sphygmomanometer was possible in low and middle-income countries,[34] further expanding the potential of this treatment to areas where medical resources are scarce.

Although not powered to detect statistical differences in secondary outcome measures, there was a strong trend towards reduced fatigue amongst the RIC group compared to sham. Adjusted between-group differences in FFS-7 at 6 weeks, 3 and 6 months ranged from 0.7 to 1.0, a similar magnitude to its MCID (0.45 to 1.2).[19] This was associated with a non-significant between group difference of 43.8 m for the 6MWT in favour of RIC (MCID for 6MWT in stroke of 44 m).[35] These early data merit further investigation in larger, appropriately powered studies. Our study raises the possibility of an interesting potential mechanism, with an emerging signal for reduced ATP depletion evident in the stroke-affected side at 6 weeks, consistent with previous data in skeletal muscle[36] following RIC. Animal models highlight at least seven different pathways through which RIC may preserve mitochondrial oxidative capacity,[15] critical for sustained muscle activity. Durand et al demonstrated that delivery of RIC for 2 weeks in stroke survivors significantly increased the duration of submaximal isometric contraction of paretic knee extensors compared to sham.[37] While no changes to peak fitness (VO_2peak) were observed in our study, there was a trend towards a reduced VE/VCO_2 slope and increased VAT. Taken together with the[31] P-MRS data, this suggests there may be an enhanced capacity for oxidative metabolism during activity, increased threshold to transition from aerobic to anaerobic respiration and accumulation of metabolic by-products potentially associated with fatigue. Post-stroke fatigue may share similar characteristics and pathogenic mechanisms to fatigue states in other neurological conditions. A randomised controlled trial recently demonstrated improvements in walking speed and distance after a single dose of RIC compared to sham in patients with multiple sclerosis, another condition for which fatigue is prevalent.[38] Such rapidity of improvement however suggests additional mechanisms, such as alterations to cerebral or muscle blood flow may also play a role. Clinical studies in stroke have previously demonstrated increased blood flow to the brain[13] and peripheral tissues[39] mediated by improved endothelial function and circulatory release of vasoactive substances (e.g. nitric oxide and adenosine) in response to the RIC stimulus. Such improvements in in endothelial reactivity and skeletal muscle perfusion may mitigate the impairment of sustained muscle contraction seen in post stroke muscle fatigue.[40] Changes in relation to cerebral blood flow may be particularly important as reductions in cortical excitation have been implicated in PSF development.[41] In our study we did not measure changes to cerebral or peripheral tissue perfusion or cortical excitation and therefore cannot comment on whether alterations in these factors contributed to fatigue perception, however these aspects could be investigated *in vivo* using techniques such as arterial spin labelling and functional MRI. While we did not measure levels of inflammatory markers in this study, RIC may also moderate the inflammatory component of PSF through its effects on reducing inflammatory mediators such as TNF-a, IL-1B, and IL-6.[42]

Although we hypothesise that the trends towards lower fatigue scores and greater walking distances may be related to RIC, it is possible that subtle differences in baseline BI and 6MWT (both slightly higher in the RIC group) may be confounding factors. However, both groups were largely independent at baseline and the adjusted mean changes in 6MWT were corrected for baseline scores. There was a higher proportion of haemorrhagic stroke in the sham group compared to RIC, the impact of this on fatigue and response to RIC is not yet clear due to the limited sample size of this pilot, but given the differing pathophysiology of the two entities this should be the focus of future study.

Of interest all of our participants with PSF exhibited improvements in fatigue scores over 6 months of their study involvement. Natural history data for fatigue are extremely limited beyond 36 months, but tend to reveal natural fluctuations that we may have encountered in our cohort.[43] However we cannot exclude any placebo effect that interactions with our researchers may have had, even in the sham condition, on self-reported scores of fatigue.

Our study had several limitations. Firstly, the sample size was small. Despite recruitment restrictions due to the COVID 19 pandemic, feasibility of RIC in PSF was nonetheless demonstrable. Generalisability of data acquired based on these small numbers is limited. Second, although we excluded patients with histories of depression or obstructive sleep apnoea we did not perform definitive testing for such conditions, nor did we exclude a potential influence of other sleep disorders on fatigue. Further, participant numbers were too small to identify particular signals of intervention efficacy in sub-groups with degrees of mood disturbance (PHQ-9), sleep apnoea (Epworth) or those with diabetes for example. Exploring such sub-groups in future work would help our understanding of RIC and optimise patient selection. Third, we could not ensure participants were truly blinded to treatment allocation, and they may have become aware of true RIC cuff pressures. However, our researchers were careful in explaining that we were investigating 'two blood pressures' rather than an active and sham group to mitigate this potential source of bias. Fourth, we relied on participant-reported completion of treatment logs for those self-delivering the intervention at home, so cannot confirm objectively that the high compliance rates were accurate. However, effects of RIC on fatigue seemed favourable irrespective of delivery method, supporting its potential as a low cost treatment that patients with PSF could use repeatedly and independently at home.

Conclusion

Remote ischaemic conditioning was safe, acceptable, and feasible for people with PSF and shows promise in terms of impact on fatigue measures, supported by biologically plausible mechanistic data. Further investigation in larger studies powered to investigate effectiveness is warranted.

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Declaration of Competing Interest

No authors have conflicts of interest to disclose.

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