Title page

Aerobic Exercise and Consecutive Task-specific Training (AExaCTT) for upper limb recovery after stroke: a randomised controlled pilot study.

Running Title: Aerobic Exercise prior to Task-specific Training

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Conflicts of interest - None

Funding was provided by a National Stroke Foundation of Australia seed grant and a Faculty of Health and Medicine research equipment grant, University of Newcastle, Australia. Sarah Valkenborghs, Milanka Visser and Katarzyna Zalewska are PhD students supported by the University of Newcastle. Sarah Valkenborghs is also funded by a Jennie Thomas Medical Research grant. In-kind support is provided by the Priority Research Centre for Physical Activity and Nutrition and the Priority Research Centre for Stroke and Brain Injury, University of Newcastle, as well as the Centre of Research Excellence in Stroke Rehabilitation and Brain Recovery, Hunter Medical Research Institute.

Aerobic Exercise and Consecutive Task-specific Training (AExaCTT) for upper limb recovery after stroke: a randomised controlled pilot study.

Abstract

Objective: This study examined the feasibility of a parallel-group assessor-blinded randomised controlled trial investigating whether task-specific training preceded by aerobic exercise (AEX+TST) improves upper limb function more than task-specific training (TST) alone.

Methods: People with upper limb motor dysfunction after stroke were allocated to TST or AEX+TST. Both groups were prescribed 60 hours of TST over 10 weeks (3 × 1h sessions with a therapist per week and 3 × 1h of home-based self-practice per week). The AEX+TST group performed 30 minutes of aerobic exercise immediately prior to the 1h of TST with the therapist. Recruitment, adherence, retention, participant acceptability, and adverse events were recorded. Clinical measures were performed pre-randomisation at baseline, on completion of the intervention, and at 1- and 6- months follow-up.

Results: 59 persons after stroke were screened, 42 met the eligibility criteria and 20 (11 male; mean (SD) age: 55.4 (16.0) years; time-since-stroke: 71.7 (91.2) months) were recruited over 17 months. The mean Wolf Motor Function Test Functional Ability Score at baseline was 27.4 (max = 75) and the mean Action Research Arm Test score was 11.2 (max = 57). Nine were randomised to AEX+TST and 11 to TST. There were no adverse events but there was one drop out. Retention at 1-month and 6-months follow-up was 80% and 85%, respectively. Attendance was 93 (6)% for the AEX+TST group, and 89 (9)% for the TST group. AEX+TST was perceived as acceptable (100%) and beneficial (87.5%). Exertional fatigue (visual analogue scale) prior to TST was worse in the AEX+TST group (3.5 [0.7] out of 10) than the TST group (1.7 [1.4] out of 10). The TST group performed 31% more repetitions per session than the AEX+TST group.

Conclusion: A subsequent phase III study is feasible, with modifications to eligibility criteria, outcome measures, and intervention delivery recommended.

Keywords: Stroke, Aerobic Exercise, Exercise, Motor learning/control, Task-specific Training

Introduction

Upper limb dysfunction is a common persistent and disabling problem after stroke (Lai, Studenski, Duncan, & Perera, 2002; National Stroke Foundation, 2012). Since upper limb dysfunction affects well-being and quality of life (Nichols-Larsen, Clark, Zeringue, Greenspan, & Blanton, 2005), it is not surprising that advancing treatments for upper limb recovery is ranked as a top ten research priority by persons after stroke and their caregivers (Pollock, St George, Fenton, & Firkins, 2014).

Task-specific training (TST) is a progressive training approach that uses practice of goal-directed, real-world, context-specific tasks that are intrinsically and/or extrinsically meaningful to the person, to enable them to undertake activities of daily living. There is low-moderate quality evidence that task-specific training may improve the upper limb motor function of persons after stroke, with effects that remain significant 6 months later (Bosch, O'Donnell, Barreca, Thabane, & Wishart, 2014; French et al., 2016; Pollock, Farmer Sybil, et al., 2014). Transcranial magnetic stimulation and functional magnetic resonance imaging have shown improvements in upper limb motor function coincide with structural and functional reorganisation of the sensorimotor cortex of the lesioned hemisphere (Richards, Stewart, Woodbury, Senesac, & Cauraugh, 2008). These neuroplastic changes may occur when frequently repeated movements reinforce network connectional patterns (Classen, Liepert, Wise, Hallett, & Cohen, 1998), particularly when repetitions are related to skill learning (Mawase, Uehara, Bastian, & Celnik, 2017). Rehabilitation aims to capitalise on and enhance neuroplasticity in peri-infarct and non-primary motor regions to stimulate recovery and increase response to motor training.

A growing body of evidence supports the use of aerobic exercise (prolonged, rhythmical activity using large muscle groups resulting in an increased heart rate) to enhance neuroplasticity (Pin-Barre, Constans, Brisswalter, Pellegrino, & Laurin, 2017; Ploughman, Austin, Glynn, & Corbett, 2015) after stroke. In addition, an accumulating body of evidence indicates that lower limb aerobic exercise can improve upper limb motor function in both neurologically intact and stroke populations. Acutely, a single session of treadmill training improves upper limb motor function in persons in the chronic stage of recovery from stroke by almost half the minimum clinically important difference (MCID) on the Action Research Arm Test (ARAT) (Lang, Edwards, Birkenmeier, & Dromerick, 2008; Ploughman, McCarthy, Bossé, Sullivan, & Corbett, 2008). Also, an 8-week program of lower limb cycling significantly improved upper limb fine motor function in persons in the chronic stage of recovery from stroke (Quaney et al., 2009). Improvements in motor skill learning and memory induced by aerobic exercise have been associated with increased peripheral blood concentrations of BDNF (McDonnell, Buckley, Opie, Ridding, & Semmler, 2013). Aerobic exercise increases BDNF (Alcantara et al., 2018; Skriver et al., 2014), which is involved with neurogenesis (Skriver et al., 2014) and neuroprotection (Schäbitz, Schwab,

Spranger, & Hacke, 1997), thereby playing an important role in stroke recovery, including facilitating functional upper limb motor rehabilitation (Schäbitz et al., 2004).

If aerobic exercise alone can enhance motor function after stroke, the emergent hypothesis is that motor learning in stroke rehabilitation may be enhanced if the brain is primed with aerobic exercise prior to motor training (Mang, Campbell, Ross, & Boyd, 2013). In animals, this hypothesis has been supported by the finding that aerobic exercise facilitated greater relearning of forelimb reaching in post-stroke animals compared with running alone, reaching alone, or no rehabilitation (Ploughman, Attwood, White, Doré, & Corbett, 2007). We previously implemented a combined aerobic exercise and task-specific training intervention to improve upper limb motor function in two people after stroke: one in the subacute and one in the chronic stage of recovery from stroke (Valkenborghs, Visser, Nilsson, Callister, & van Vliet, 2018). This phase I study demonstrated that the combined intervention was feasible and perceived as acceptable and beneficial. Participants improved their upper limb motor function on the ARAT (subacute participant = 4 points; chronic participant = 2 points) and WMFT (subacute participant = 5 points; chronic participant = 3 points). Participants also improved their aerobic fitness (subacute participant = +4.66 mL O_2/kg/min; chronic participant = +7.34 mL O_2/kg/min) and 6-minute walking distance (subacute participant = +50 m; chronic participant = +37 m), and the prevailing feedback from participants was that they would like to exercise at a higher intensity.

In line with the progressive staging of pilot studies to evaluate complex motor interventions (Craig et al., 2008; Dobkin, 2009), the purpose of this phase II study was to investigate the feasibility of a randomised controlled trial comparing combined aerobic exercise and consecutive task-specific training (AEX+TST) to task-specific training (TST) alone to improve upper limb function after stroke.

Methods

Study Design

This was a parallel-group assessor-blinded randomised controlled pilot study. The design and methods have been reported in detail previously (Valkenborghs et al., 2017). In summary, people after stroke were randomised to a control group who performed task-specific training (TST) alone or an experimental group who performed aerobic cycling exercise prior to task-specific training (AEX + TST). The intervention sessions were supervised by a therapist 3 days per week for 10 weeks (the program was increased from 8 weeks due to feedback from case series participants). Both groups were also provided with an individually-prescribed home-based task-specific training program. Assessments were conducted prior to randomisation at baseline, within 1 week of the end of the intervention (primary timepoint), and 1 and 6 months following the intervention

period. This study was approved by Hunter New England Human Research Ethics Committee (14/12/10/4.07) and registered with the University of Newcastle Human Research Ethics Committee (H-2015-0105). The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12616000848404).

Participants and intervention

20 people after stroke were recruited from a variety of community-based sources including the Hunter Medical Research Institute volunteer register, by advertisement on the website of the National Stroke Foundation and Stroke Recovery Association of New South Wales, and University of Newcastle and Hunter Medical Research Institute social media networks. The eligibility criteria are presented in Table 1. To obtain balanced groups with respect to severity of functional impairment, computer-generated 2-4-6 block randomisation was used with stratification using scores on the ARAT (Group 1: score 0–3; Group 2 score 4–28; Group 3 score 29–56) (Morris et al., 2008; Sealed Envelope Ltd, 2012). Randomisation was concealed and performed by the trial coordinator via the REDCap system (Harris et al., 2009).

< Insert Table 1 – Eligibility Criteria here >

Interventions

Task-specific Training

Participants in both groups performed 30 hours of supervised task-specific training and were prescribed an additional 30 hours of home-based practice. The aim was to perform 100-300 repetitions of tasks per hour prescribed according to individual goals. Where required, part-practice of everyday skills was performed (e.g., extend elbow and flex shoulder to reach to cup, open fingers and thumb to grasp cup, flex elbow and shoulder to transfer cup to mouth). Appropriate tasks were selected from an upper limb task-specific training manual and adapted based on the individual participant's needs (Cunningham, Turton, Van Wijck, & Van Vliet, 2015). Each task was varied in terms of the shape, size, weight, and texture of the object(s), and the distance, speed and direction of the movement(s). The difficulty of each component task was graded, reviewed and progressed according to the individual ability of the participant, so that they could perform the task successfully without requiring the use of compensatory strategies. The number of repetitions was inclusive of performance of part practice and whole practice of tasks. Each repetition was observed and

recorded in a task training log. Participants (or their carers) also recorded the number of repetitions and time spent on each activity during home-based practice in weekly log-sheets which were returned during the first visit of each week.

Aerobic Exercise

As discussed in Valkenborghs et al. (2017), a high-intensity interval approach was selected for its potential to enhance neuroplasticity, motor function, and adherence. Therefore, participants were prescribed 4 × 4-minute intervals of high-intensity exercise (85% of HR_{max}) with a 3-minute active recovery (70% of HR_{max}) period between each interval per 30-minute session (Askim et al., 2014). The aerobic exercise was performed on a low entry level upright (928G3, Monark, Sweden) or semi-recumbent (RT2, Monark, Sweden) cycle ergometer depending on individual ability and impairment. The initial workload was prescribed based on data from an incremental cycle ergometer test performed prior to starting the training program. Heart rate was monitored via a chest heart rate monitor (T31, Polar, Australia)) and was recorded by research assistants in the last 15 seconds of each interval.

Assessments

Specific feasibility objectives included: rate of recruitment, compliance with the program, adherence to the intervention protocols, acceptability of the modified intervention, exertional fatigue prior to TST, rate of retention, frequency of adverse events, and collection of data to inform power calculations to estimate the sample size for a subsequent larger phase III efficacy trial. Exertional fatigue was measured by the visual analogue scale for fatigue once a week prior to TST component of the session. Acceptability of AEX+TST was assessed by means of a dichotomous questionnaire administered within one week of completion of the intervention program.

The primary clinical outcomes were scores on the ARAT and the WMFT for upper limb motor function, administered according to standardised protocols (Morris, Uswatte, Crago, Cook, & Taub, 2001); Platz et al. (2005). The same blinded physiotherapist performed all assessments and was based at a different site than the staff delivering the intervention to minimise risk of unblinding.

The Motor Activity Log (MAL) was used to assess the perceived amount and quality of use of the affected upper limb (Uswatte, Taub, Morris, Light, & Thompson, 2006). The Stroke Impact Scale (SIS) assessed

multidimensional self-reported stroke outcomes, including strength, hand function, activities of daily living, mobility, communication, emotion, memory and thinking, and participation (Duncan et al., 1999).

Aerobic fitness was assessed by means of an incremental cycle ergometer test during which oxygen consumption was measured by a portable metabolic system (K4b2, Cosmed Asia-Pacific Pty Ltd, Artarmon, NSW, Australia), and cardiac rhythm and heart rate were measured by a portable ECG (Quark T12, Cosmed Asia-Pacific Pty Ltd, Artarmon, NSW, Australia). Criteria for attainment of VO_{2max} were 1) plateau in oxygen consumption despite an increase in workload, and 2) R-value >1.1. Indications of volitional exhaustion and attainment of ≥85% of age-predicted HR_{max} (220-age) were also recorded. The 6-Minute Walk Test (6MWT) was performed in accordance with the American Thoracic Society Guidelines (except that it was on a 20m corridor due to space restrictions (Dunn et al., 2015)) to assess functional fitness (American Thoracic Society Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002).

Although participants were asked not to alter their levels of physical activity during the trial, the International Physical Activity Questionnaire (IPAQ) was administered to determine any changes in physical activity levels over the study period (Booth et al., 2003). The Fatigue Assessment Scale (FAS) was also administered to detect any changes in fatigue levels over the course of the study (Mead et al., 2007).

Peripheral blood serum mature BDNF concentrations were measured using a commercial enzyme-linked immunosorbent assay (CE Marked BDNF Rapid, BEK-2211-1P-CE, ELISA Kit, Biosensis) by a blinded researcher, as described previously (Valkenborghs et al., 2017).

Analysis

Feasibility data are reported using descriptive statistics. The mean within-group changes over time and standard deviation for each group were calculated for the clinical measures. The effect size of the difference in between-group change over time was calculated using Cohen's *d*. An intention to treat approach was used with the last observation carried forward for missing data. As this is a phase II study, it is not designed (nor powered) to assess efficacy, and therefore significance testing was not undertaken (Dobkin, 2009; Lancaster, 2015).

Results

The flow of participants through the study is shown in Figure 1. 59 potential participants were screened, 42 met the eligibility criteria and 20 (11 male; mean (SD) age: 55.4 (16.0) years; time-since-stroke: 71.7 (91.2) months) provided informed written consent and commenced the study over 17 months (100% of target, 48%

of eligible potential participants). All participants were recruited from the community with the most successful recruitment sources being social media, word of mouth, and Hunter Medical Research Institute volunteer register. Nine were randomised to AEX + TST and 11 to TST alone. There were no adverse events but there was one dropout from the AEX+TST group due to bronchitis. Retention at 1-month and 6-month follow-up was 80% and 85%, respectively. Attendance at supervised sessions for participants (excluding dropout) was 93(6)% in the AEX + TST group and 89(9)% in the TST group.

< Insert Figure 1 - Study Flow Diagram here >

Table 2 presents participant characteristics at baseline. The mean WMFT FAS score was 27.4 (out of 75) and the mean ARAT score was 11.2 (out of 57) with the majority (55%) of participants falling in to the most impaired ARAT Group 1 (0-3). Although the groups were balanced at baseline, there was a trend towards a significant difference between groups for age and time since stroke (p = 0.08 for both).

< Insert Table 2 – Participant characteristics at baseline here >

The aerobic exercise training protocol required adaptation during the study to make it feasible for more severe and non-ambulatory participants. Instead of exercising at 85%HR_{max}, the mean %HR_{max} at the end of each interval was 72±14% for the higher intensity interval and 57±21% instead of 70%HR_{max} for the recovery interval. The mean peak training %HR_{max} was 88±12%, with all participants except one achieving ≥85% HR_{max} at least once during the program, with the mean number of times being 28±49 of the 120 intervals over the 30 sessions. The mean change in training workload over the 10 weeks was 11.2±11.5W (27±28%) for the higher intensity interval and 4.0±7.7W (17±33%) for the recovery interval.

The mean (SD) level of exertional fatigue reported by participants in the AEX+TST group was 3.5 (0.7) out of 10 whereas the TST group was 1.7 (1.4) out of 10. The mean (SD) number of repetitions performed per 1-hour of supervised task-specific training was 158 (49) for the AEX+TST group and 208 (8) for the TST group. The amount of home-based practice performed relative to the total prescribed was reported to be 73.8 (30.9) % for the AEX+TST group and 69.1 (36.7) % for the TST group.

All AEX+TST participants who completed the training (n=8) reported that the combined aerobic exercise and task-specific training intervention was acceptable. The acceptability of specific aspects of the combined intervention was further explored, and the results have been presented in Table 3. Participants were also asked to provide suggestions for program improvement. Responses to this question were:

- "Sometimes [the] exercise is too hard. [I'm] Left too fatigued to do hand practice."
- "Would have preferred to do [a shorter program] e.g., 5 weeks with a 1-2 week break before completing final 5 weeks (to allow [my] arm to rest as it got tired)."
- "[I would like a shorter program] 8 weeks"
- "[I would like] More days (5 days per week)"

< Insert Table 3 - Acceptability of aerobic exercise combined with task-specific training here >

Both groups made similar small improvements in motor function during the 10-week intervention as measured by the ARAT and the WMFT (Table 4 and Table 5). At 1-month and 6-month follow-up, both groups had comparable retainment of improvements on the ARAT but the TST group had better retainment than the AEX+TST group on the WMFT. These results indicated change greater than a MCID (3 points) on the WMFT for the TST group at the end of the intervention (d = 0.72), 1-month follow-up (d = 0.82), and at 6-month follow-up (d = 1.26)(Lin et al., 2009).

< Insert Table 4 – Outcome measures at each timepoint here >

< Insert Table 5 - Change scores of outcome measures and effect sizes of differences in changes between groups here >

< Insert Table 6 - Per protocol pre- and post- intervention mean (standard deviation) according to ARAT group here >

Self-reported upper limb use (MAL AOU and MAL QOM) changed by a MCID (1.0-1.1) (Lang et al., 2008) for the TST group at 6 months but there were no changes for either group at any other timepoint.

This contrasted with results for the hand use domain of the SIS which, although they did not reach a MCID (17.8) (Lin et al., 2010), strongly favoured the AEX+TST group at each time point and demonstrated a medium effect size at 1 month follow up (*d* = 0.62) and a small effect size at 6-month follow up (*d* = 0.43). Self-reported strength improved in both groups with a larger increase in the TST group than the AEX+TST group; the TST group had more than a MCID (9.2 points) at the end of the 10-week intervention (*d* = 1.43) and 1 month later (*d* = 0.85) (Lin et al., 2010). Both groups reported a MCID in mobility (4.5 points) (Lin et al., 2010) with the TST group reporting approximately twice as much improvement at the end of the intervention (*d* = 0.52) whereas the AEX+TST group reported better retainment of their improvement at both the 1-month and 6-month follow-up (*d* = 0.32) assessments. Both groups made small improvements in self-reported activities of daily living during the intervention, with the AEX+TST group reporting better retainment of their improvement at both the 1-month (*d* = 0.40) and 6-month follow-up (*d* = 0.56) assessments. Both groups reported similar improvements in communication at all time points relative to baseline, except at 6 months where the AEX+TST group reported nearly twice as much improvement as the TST group (*d* = 0.27). The AEX+TST group improved more than the TST group in self-reported participation of activities after the intervention (*d* = 0.75), at 1-month follow-up (*d* = 0.808), and at 6-month follow-up (*d* = 0.33). There were similar findings for self-reported memory with the AEX+TST group improving more than the TST group after the intervention (*d* = 0.59), at 1-month follow-up (*d* = 0.49), and at 6-month follow-up (*d* = 0.66). Self-reported mood also improved more in the AEX+TST group than the TST group after the intervention (*d* = 0.41), at 1-month follow-up (*d* = 0.79), and at 6-month follow-up (*d* = 0.92).

Although the AEX+TST group was classified as having post-stroke fatigue at baseline (Cumming & Mead, 2017), they had improved by more than a MCID (3.0 points) (de Kleijn, De Vries, Wijnen, & Drent, 2011) at the end of the intervention (*d* = 0.58). The AEX+TST group showed a further improvement at 1-month follow-up (*d* = 0.94) and they had still retained a MCID at the 6-month follow-up relative to baseline (*d* = 0.58). The TST group were not classified as fatigued at baseline and had trivial fluctuations in FAS score between each timepoint. Level of physical activity, as reported on the IPAQ, was low-moderate for both groups and remained consistent across the program.

The AEX+TST group improved peak oxygen consumption more than the TST only group at the end of the intervention (*d* = 0.31), 1-month follow-up (*d* = 0.33) and 6 -month follow-up (*d* = 0.21), and the improvement exceeded a MCID (2mL/kg/min) at the end of the intervention and 1-month follow-up (Marsden, Dunn, Callister, Levi, & Spratt, 2013). The AEX+TST group had a larger increase in R-value than the

TST-group at the end of the intervention (*d* = 0.773), 1-month follow-up (*d* = 0.33), and 6-month follow-up (*d* = 0.21). The AEX+TST group also had a larger increase in peak workload than the TST-group at the end of the intervention (*d* = 0.51), 1-month follow-up (*d* = 0.29), and 6-month follow-up (*d* = 0.36). All participants cycled until volitional exhaustion. Data for the other three criteria are presented in Table 7. There were no notable changes in functional fitness as measured by distance covered during the 6MWT for either group between any timepoints. BDNF levels decreased in both groups, more so in the TST-group than the AEX+TST group.

< Insert Table 7 - Attainment of VO_2max criteria here >

Discussion

This study has provided important feasibility data including information on recruitment (34% of those screened), attendance (93 [6]% and 89 [9]% of supervised sessions for the AEX+TST group and TST group, respectively)), retention (95% completion of those randomised), as well as adherence and acceptability (100%) of the intervention. Overall, these elements of feasibility were all very positive and indicate the possibility of a phase III trial. Some of the components that may need to be re-considered include the eligibility criteria, measurement of impairment, and level of exertional fatigue after aerobic exercise prior to performance of task-specific training.

Although the rates of recruitment are comparable, and in many cases favourable, to other stroke rehabilitation research studies (Durham et al., 2014; Hollands et al., 2015; Mares et al., 2014; Stinear, 2016; Turton et al., 2013), it must be noted that there were very broad inclusion criteria which meant that 71% of those screened were eligible, while 48% of those eligible were randomised. Lack of transportation was one of the reasons for refusal to participate and has previously been identified in the stroke literature as a major barrier to recruitment (Gomes, Michaelsen, Rodrigues, Farias, & Silva, 2015). As can be seen in table 6, regardless of intervention group, participants in ARAT group 1 did not improve upper limb motor function on either the ARAT or the WMFT. This might indicate that the eligibility criteria for a future phase III trial may need to be adjusted to exclude participants who fall in to ARAT group 1 at the point of screening, as they do not appear

to benefit from this intervention in terms of upper limb motor function (Houwink, Nijland, Geurts, & Kwakkel, 2013). There were inconsistent results on the ARAT and WMFT in terms of which group improved upper limb motor function most. Therefore, we have not obtained data that can be used to inform a sample size calculation for a subsequent phase III trial and it is also difficult to establish which assessment would be better suited as the primary outcome measure. The WMFT is more sensitive to changes in motor impairment than the ARAT as it involves grasping objects in a greater variety of functional tasks, and it includes several proximal arm movements not requiring grasp. This may reflect why more improvement was detected for the TST group than the AEX+TST group on the WMFT, but not on the ARAT. Although both groups adhered to the TST intervention protocol well and achieved the target of 100-300 repetitions per session, given the TST group performed an average of 31% more repetitions per session than the AEX+TST group, this is not an implausible outcome.

The fewer repetitions achieved by the AEX+TST group may be a reflection of their increased exertional fatigue (3.5 [0.7] out of 10) prior to task-specific training compared to the TST group (1.7 [1.4] out of 10) which exceeded a MCID (1.13-1.26) on the visual analogue scale for exertional fatigue (Khanna et al., 2008). As outlined in the paper describing the protocol for this trial (Valkenborghs et al., 2017) the aerobic exercise protocol was adapted to high-intensity interval training as it appeared to be the optimal intensity to use both in terms of improving motor function and participant acceptability from our previous stage I study (Valkenborghs et al., 2018). However, given the increased exertional fatigue and decreased number of repetitions performed by the AEX+TST group, it is conceivable that the intensity of the aerobic exercise compromised participants' ability to perform TST. Furthermore, this was a point raised by one participant on the acceptability questionnaire. Although aerobic exercise appeared to compromise subsequent performance of task-specific training, despite performance of fewer repetitions, it did not appear to have any adverse consequences on motor learning or motor retention in the AEX+TST group. In a similar small (n = 17) study that compared forced aerobic exercise prior to TST, voluntary aerobic exercise prior to TST and TST alone, participants performed 225-400 reps per 45-minute session which is substantially more than our participants performed (158 (49) for the AEX+TST group and 208 (8) for the TST group) per 60-minute session (Linder, Rosenfeldt, Dey, & Alberts, 2017). However, despite finding improvement in impairment for all groups, particularly the forced exercise group, there was no improvement on function as measured by the WMFT. It is also worth noting that this was a less chronic and less impaired sample. One suggestion for a future phase III trial may be to include a measure of impairment such as the Fugl-Meyer scale, as recommended by the Stroke Recovery and Rehabilitation Roundtable (Kwakkel et al., 2017).

Another approach may be to alter the order of the combined interventions. Although recent literature supports the effectiveness of higher intensity interval aerobic exercise in the enhancement of neuroplasticity

and functional recovery after stroke compared to moderate intensity training (Pin-Barre et al., 2017), it also suggests that it may be more effective after motor training instead of prior to motor training (Nepveu et al., 2017; Roig, Skriver, Lundbye-Jensen, Kiens, & Nielsen, 2012). Therefore, a recommendation for a future phase II trial might be for participants to perform the aerobic exercise after completion of task-specific training.

Otherwise the AEX+TST intervention was deemed very acceptable on all domains examined. Interestingly, of the 87.5% of participants that reported the intervention to be beneficial, an almost equal proportion reported the main benefits to be psychosocial in nature (71.4%) relative to movement (75%). Data from the SIS scale would support that the aerobic exercise benefitted the AEX+TST group in a number of domains which rank highly as research priorities including fatigue, mood, memory and communication (Mead, Bernhardt, & Kwakkel, 2012; Pollock, St George, et al., 2014; Saunders, Greig, & Mead, 2014). These benefits were not enjoyed by the TST group. The AEX+TST also improved their cardiorespiratory fitness more than the TST group which is an important risk factor in the prevention of stroke (Hussain et al., 2018; Pandey et al., 2016). These findings support the merit of including aerobic exercise as part of a comprehensive stroke rehabilitation intervention (Collins, Clifton, Wijck, & Mead, 2018; Gezer, Karaahmet, Gurcay, Dulgeroglu, & Cakci, 2018).

Conclusions

Overall a future phase III randomised controlled trial appears feasible with respect to recruitment, adherence, acceptability, retention and adverse events. Modifications to the eligibility criteria may be appropriate to exclude persons who are classified as ARAT group 1. It may also be valuable to include a measure of impairment such as the Fugl-Meyer scale. Given the 31% more repetitions performed by the TST group, there may be merit in allowing the AEX+TST group a rest period after the aerobic exercise. Alternatively, a phase II study could investigate the performance of aerobic exercise after task-specific training for the upper limb in persons after stroke as another potential solution.

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Tables

Table 1 - Eligibility Criteria

Inclusion Criteria
• ≥16 years old • Clinical diagnosis of ischaemic or haemorrhagic stroke • Upper limb movement deficit, i.e. score <63 on the WMFT or <52 on the ARAT • Able to undertake aerobic exercise training • GP medical clearance
Exclusion Criteria
• Upper limb movement deficits attributable to non-stroke pathology • Unable to lift hand off lap when asked to place hand behind head (gross motor task from the ARAT) • Severe fixed contractures of elbow or wrist (i.e. grade 4 on the modified Ashworth scale) • Moderate to severe receptive aphasia (< 10 on 'receptive skills' of Sheffield Screening Test for Acquired Language Disorders)

Table 2 – Participant characteristics at baseline. Data are mean (SD) or n(%).

	AEX+TST (n=9)	TST (n=11)	Total (n=20)
Age (years)	62.1 (11.7)	49.8 (17.4)	55.4 (16.0)
Male	5 (56)	6 (55)	11 (55)
Months since stroke	34.6 (46.3)	102.2 (108.8)	71.7 (91.2)
Left-sided lesion	6 (67)	8 (73)	14 (70)
Paresis of pre-stroke dominant side	6 (67)	9 (82)	15 (75)
ARAT Group 1 (0–3)	6 (67)	5 (45)	11 (55)
ARAT Group 2 (4–28)	1 (11)	2 (18)	3 (15)
ARAT Group 3 (29–56)	2 (22)	3 (27)	5 (25)
ARAT Score	9.7 (12.4)	12.6 (17.2)	11.2 (14.9)
WMFT Score	24.3 (8.9)	29.9 (15.4)	27.4 (12.9)
WMFT Time (seconds)	1497 (804)	1114 (601)	1286 (708)
MoCA	22 (5)	19.1 (8.5)	20.3 (7.2)
Star Cancellation	45.9 (18.7)	52.9 (3.1)	49.7 (12.7)
FAS	28.1 (8.0)	20.5 (5.9)	23.7 (7.8)
IPAQ	1.8 (0.7)	1.9 (0.7)	1.8 (0.7)
VO_2peak (mL/kg/min)	13.0 (4.5)	16.1 (5.6)	14.7 (5.2)
6MWT (m)	131.2 (107.5)	301.1 (129.4)	229.6 (145.7)

ARAT = Action Research Arm Test (max = 57); WMFT = Wolf Motor Function Test (max = 75), MoCA = Montreal Cognitive Assessment (max = 30; normal ≥ 26); FAS = Fatigue Assessment Scale (max = 50; fatigue cut-off ≥24); IPAQ = International Physical Activity Questionnaire (1 = low, 2 = moderate, 3 = high); VO2peak = peak oxygen consumption; kg = kilogram; mL = millilitres; min = minute. 6MWT = Six Minute Walk Test); m = metres; s = seconds.

Table 3 - Acceptability of aerobic exercise combined with task-specific training

Question	**% Yes**
Overall, did you find the intervention acceptable?	100%
Did you benefit from the intervention? *If yes, did the benefits you experienced relate to:* - *Movement/Physical well-being* - *Psychological/Social well-being* - *Other*	87.5% *75%* *71.4%* *0%*
Do you feel the benefits you gained were worth the time you invested?	75%
Compared to your usual/previous therapy, did you find the combination of aerobic exercise and hand/arm training acceptable?	100%
Was the order of therapy (aerobic exercise followed by hand/arm training) acceptable?	87.5%
Did you find the frequency (3 days per week) of the sessions acceptable? *If no, would you have preferred them to be:* *a) More often* b) *Less often*	62.5% *37.5%* *0%*
Did you find the duration of the individual sessions (1.5 hours) acceptable? *If no, would you have preferred them to be:* *a) Longer* b) *Shorter*	75% *25%* *0%*
Did you find the amount of practice in the individual sessions acceptable? *If no, would you have preferred* *a) More practice* b) *Less practice*	75% *12.5%* *12.5%*
Did you find the duration of the entire program (10 weeks) acceptable? *If no, would you have preferred it to be:* *a) Longer* b) *Shorter*	75% *12.5%* *12.5%*

Table 4 – Outcome measures at each timepoint

	AEX+TST				TST			
	Pre	*Post*	*1 month*	*6 months*	*Pre*	*Post*	*1 month*	*6 months*
ARAT	9.7 (12.4)	11.8 (14.3)	12.1 (14.0)	11.8 (14.3)	12.4 (17.2)	14.6 (18.0)	14.7 (20.1)	14.8 (19.7)
WMFT	24.3 (8.9)	25.8 (9.6)	26.7 (9.4)	27 (9.7)	29.9 (15.4)	33.7 (15.4)	35.3 (17.6)	37.4 (18.4)
WMFT Time (s)	1358 (557)	1324 (560)	1262 (562)	1272 (578)	1159 (617)	1069 (636)	1042 (640)	1002 (628)
MAL (AOU)	0.61 (0.78)	0.84 (0.65)	1.1 (1.1)	1.3 (1.4)	0.9 (1.2)	1.2 (1.3)	1.6 (1.6)	1.5 (1.8)
MAL (QOM)	1.6 (1.0)	1.8 (1.1)	1.7 (1.1)	2.0 (0.7)	1.6 (1.4)	1.9 (1.3)	1.8 (1.2)	2.3 (1.3)
SIS								
- Strength	23.4 (11.4)	26.9 (14.6)	27.4 (12.0)	32.8 (10.9)	35.9 (19.1)	48.6 (17.6)	53.6 (23.3)	45.0 (20.5)
- Memory	53.0 (20.2)	66.0 (11.)	69.2 (10.6)	65.7 (12.7)	58.7 (17.9)	63.4 (15.0)	67.5 (10.0)	61.8 (15.6)
- Mood	39.2 (18.9)	50.1 (18.7)	55.3 (15.3)	53.6 (18.2)	58.4 (16.9)	64.9 (12.7)	64.4 (15.5)	58.4 (11.9)
- Communication	51.1 (27.1)	54.6 (21.7)	57.5 (22.5)	59.4 (21.2)	54.0 (24.4)	56.6 (21.6)	61.3 (18.2)	58.7 (18.7)
- ADL	43.8 (11.5)	48.3 (13.4)	47.8 (11.3)	49.6 (12.0)	58.4 (17.3)	63.5 (9.7)	59.3 (14.6)	58.6 (17.3)
- Mobility	51.1 (12.4)	56.3 (13.3)	59.0 (14.2)	59.0 (15.1)	61.0 (16.1)	71.3 (7.7)	67.7 (16.3)	63.8 (11.9)
- Hand Use	8.4 (18.6)	11.6 (19.7)	13.3 (21.0)	18.7 (26.6)	27.3 (30.6)	25.8 (28.6)	16.3 (22.5)	24.0 (23.6)
- Activities	25.3 (14.1)	44.2 (15.8)	46.9 (11.6)	37.5 (16.4)	49.1 (23.1)	54.32 (13.0)	50.5 (22.4)	55.0 (17.7)
FAS	28.1 (8.0)	24.4 (6.7)	22.3 (5.9)	25 (6.9)	20.5 (5.9)	20.6 (7.5)	19.9 (4.7)	20.4 (6.6)
IPAQ	1.8 (0.7)	1.8 (0.5)	1.6 (0.5)	1.4 (0.5)	1.9 (0.7)	2.1 (0.7)	1.9 (0.5)	1.8 (0.8)
VO_2peak (mL/kg/min)	13.0 (4.5)	15.3 (3.8)	16.0 (4.0)	13.5 (4.3)	16.1 (5.6)	17.6 (5.8)	18.6 (6.30	15.6 (6.6)
Peak HR (% HR_{max})	77 (17)	79 (14)	82 (16)	79 (14)	82 (9)	83 (7)	79 (13)	85 (13)
Peak Workload (W)	68 (33)	84 (37)	84 (33)	81 (30)	100 (32)	108 (40)	111 (53)	105 (55)
R-value	1.09 (0.17)	1.22 (0.17)	1.20 (0.16)	1.21 (0.14)	1.22 (0.1)	1.22 (0.15)	1.28 (0.1)	1.29 (0.18)
6MWT (m)	131.2 (107.5)	130.5 (102.7)	144.0 (113.1)	142.9 (103.3)	301.1 (129.4)	303.6 (115.0)	315.9 (114.1)	299.6 (113.7)
BDNF (ng/mL)	24.1 (12.9)	20.4 (12.1)	-	-	22.4 (12.6)	17.7 (8.7)	-	-

ARAT = Action Research Arm Test (max = 57); WMFT = Wolf Motor Function Test (max = 75); s = seconds; MAL = Motor Activity Log (max = 5); AOU = Amount of Use; QOM = Quality of Movement; SIS = Stroke Impact Scale (max = 80); ADL = Activities of Daily Living; FAS = Fatigue Assessment Scale (max = 50; fatigue cut-off ≥24); IPAQ = International Physical Activity Questionnaire (1 = low, 2 = moderate, 3 = high); VO_2peak = peak oxygen consumption; mL = millilitres; kg = kilogram; min = minute; % HR_{max} = percentage of age-predicted maximal heart rate; W = Watts; 6MWT = Six Minute Walk Test; m = metres.

Table 5 - Change scores of outcome measures and effect sizes of differences in changes between groups

		AEX+TST			TST		
	MCID	*Post – Pre*	*1 month - Pre*	*6 month - Pre*	*Post - Pre*	*1 month - Pre*	*6 month - Pre*
ARAT	5.7	2.1 (3.5) *	2.4 (3.4)	2.1 (3.5)	0.8 (2.5)	2.1 (4.1)	2.2 (3.7)
WMFT FAS	3	1.4 (3.2)	2.3 (3.2)	2.7 (3.3)	3.8 (3.6) §#	5.4 (4.5)+	7.5 (4.5) §+
WMFT Time (s)	22.5-30	-34.5 (170.6) §	-96.1 (193.8) §	-86.4 (204.5) §	-90.0 (160.3) §*	-117.7 (140.7) §	-157.3 (217.2) §*
MAL (AOU)	1.0-1.1	0.2 (1.2)	0.5 (1.6)	0.5 (1.7)	0.3 (0.4)	0.7 (0.9)	0.6 (1.1)
MAL (QOM)	1.0-1.1	0.2 (1.6)	0.1 (2.0)	0.2 (0.7)	0.3 (0.6)	0.2 (0.9)	1.2 (1.1) +
Stroke Impact Scale							
Strength	*9.2*	3.5 (5.0)	4.0 (3.2)	8.3 (6.1)	12.7 (7.9) §+	17.7 (22.6) §+	9.1 (12.0)
Memory	-	12.0 (16.5) #	16.1 (18.9) *	12.7 (17.6) #	4.7 (9.5)	8.8 (12.6)	3.1 (13.2)
Mood	-	10.9 (11.8) *	16.0 (12.0) #	13.8 (15.1) +	6.5 (10.7)	6.1 (14.0)	0.0 (16.5)
Communication	-	3.5 (12.0)	6.3 (18.2)	8.3 (17.4) *	2.6 (8.1)	7.3 (10.3)	4.7 (10.2)
ADL	*5.9*	4.4 (15.3)	4.0 (11.0) *	5.8 (13.8) #	5.1 (13.7)	0.9 (5.0)	0.2 (7.1)
Mobility	*4.5*	5.2 (5.1) §	7.9 (8.4) §	7.9 (6.3) §#	10.3 (13.2) §#	6.7 (8.1) §	2.8 (8.2)
Hand Use	*17.8*	3.1 (25.2)	4.9 (28.1) #	10.2 (34.1) *	-1.5 (37.3)	-10.9 (25.6)	-3.3 (32.3)
Activities	-	18.9 (21.4) #	21.7 (21.6) +	12.2 (20.3) *	5.2 (17.4)	1.4 (29.8)	5.9 (19.6)
FAS	*3*	-3.9 (8.9) §#	-5.8 (7.6) §+	-3.3 (7.5) §#	0.2 (5.0)	-0.5 (4.2)	0.5 (6.3)
IPAQ	-	0 (0.7)	-0.1 (0.8)	-0.1 (0.9)	0.2 (0.8)	0.0 (0.6)	-0.1 (0.9)
VO_2peak (mL/kg/min)	*2*	2.3 (2.9) §*	3.0 (2.6) §	0.5 (3.5) *	1.5 (2.6)	2.5 (2.7) §	-0.5 (3.5)
6MWT (m)	*50*	-0.7 (17.7)	12.8 (14.7)	11.6 (25.3) *	2.5 (36.0)	14.8 (41.20)	-1.5 (52.6)
Peak HR (% HR_{max})	-	3 (10)*	6 (7)+	4 (3)*	0 (6)	- 4 (15)	2 (12)
Peak Workload (W)	-	17 (23)#	17 (17)*	14 (18)*	8 (14)	11 (25)	5 (31)
R-value	-	0.11 (0.15)#	0.09 (0.17)*	0.08 (0.10)*	-0.0 (0.15)	0.05 (0.08)	0.05 (0.18)
BDNF (ng/mL)	-	-3.7 (14.5)	-	-	-4.7 (12.1)	-	-

§Change ≥ MCID; *d ≥ 0.2; #d ≥ 0.5; +d ≥ 0.8; mean (standard deviation); 6MWT = Six Minute Walk Test; AOU = Amount of Use; ARAT = Action Research Arm Test (max = 57); FAS = Fatigue Assessment Scale (max = 50; fatigue cut-off ≥24); IPAQ = International Physical Activity Questionnaire (1 = low, 2 = moderate, 3 = high); kg = kilogram; m = metres; MAL = Motor Activity Log (max = 5); mL = millilitres; min = minute; MoCA = Montreal Cognitive Assessment (max = 30; normal ≥ 26); QOM = Quality of Movement; s = seconds; SIS = Stroke Impact Scale (max = 80); VO_2peak = peak oxygen consumption; WMFT = Wolf Motor Function Test (max = 75).

Table 6 - Per protocol pre- and post- intervention mean (standard deviation) according to ARAT group

		ARAT			WMFT			WMFT Time (s)		
ARAT Group	**Group**	*Pre*	*Post*	*Δ*	*Pre*	*Post*	*Δ*	*Pre*	*Post*	*Δ*
1	*AEX+TST*	2.0(1.5)	2.5(1.2)	0.5(1.2)	19.2(4.3)	19.8(3.4)	0.7(2.7)	1680(211)	1679(177)	-1(112)
	TST	2.5(1.2)	2.8(1.6)	0.3(1.7)	23.0(5.2)	26.2(7.9)	3.2(6.8)	1456(198)	1394(319)	-62(201)
2	*AEX+TST*	12.0(0.0)	24(0.0)	9.0(0)	30.0(0.0)	38.0(0.0)	8.0(0.0)	1157(0)	746(0)	-411(0)
	TST	4.0(0.0)	4(0.0)	0.0(0)	19.5(10.6)	25.5(3.5)	6.0(7.1)	1645(102)	1478(47)	-167(55)
3	*AEX+TST*	29.0(0.0)	36(0.0)	7.0(0)	41.0(0.0)	42.0(0.0)	1.0(0.0)	273(0)	382(0)	109(0)
	TST	38.7(6.4)	41.0(10.4)	2.3(4.0)	50.7(12.7)	54.3(11.9)	3.7(4.0)	242(195)	148(89)	-94(133)

ARAT = Action Research Arm Test (max = 57); WMFT = Wolf Motor Function Test (max = 75); s = seconds; 1 = 0-3; 2 = 4-28; 3 = 29-57;

Table 7 - Attainment of VO_2max criteria

Timepoint	**Group**	**VO_2 Plateau**	**R-value ≥1.1**	**Volitional Exhaustion**	**≥85% HR_{max}**
Pre	*AEX+TST*	0%	50%	100%	33%
	TST	44%	89%	100%	56%
Post	*AEX+TST*	50%	83%	100%	43%
	TST	33%	89%	100%	33%
1-month	*AEX+TST*	50%	83%	100%	50%
	TST	33%	89%	100%	33%
6-months	*AEX+TST*	33%	83%	100%	17%
	TST	33%	89%	100%	78%

VO2 = oxygen consumption; HR_{max} = age-predicted heart rate maximum.