

# A pilot randomized controlled trial to evaluate the benefit of the cardiac rehabilitation paradigm for the non-acute ischaemic stroke population

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**Objective:** To evaluate risk factor reduction and health-related quality of life following a 10-week cardiac rehabilitation programme in non-acute ischaemic stroke subjects.

**Design:** Single-blinded randomized control trial.

**Setting:** Outpatient rehabilitation.

**Subjects:** Forty-eight community-dwelling ischaemic stroke patients (38 independently mobile, 9 requiring assistance, 1 non-ambulatory) were randomly assigned to intervention or control groups by concealed allocation.

**Intervention:** The trial consisted of a 10-week schedule with measures taken at weeks 1 and 10. Both groups continued usual care (excluding aerobic exercise); intervention subjects attended 16 cycle ergometry sessions of aerobic-training intensity and two stress-management classes.

**Main outcome measures:** Cardiac risk score (CRS);  $\text{VO}_2$  (mL  $\text{O}_2$ /kg per minute) and Borg Rate of Perceived Exertion (RPE) assessed during a standardized ergometry test; Hospital Anxiety and Depression Scale (HADS); Frenchay Activity Index; Fasting Lipid Profiles and Resting Blood Pressure.

**Results:** Group comparison with independent *t*-tests showed significantly greater improvement at follow-up by intervention subjects than controls in  $\text{VO}_2$  (intervention  $10.6 \pm 1.6$  to  $12.0 \pm 2.2$ , control  $11.1 \pm 1.8$  to  $11.1 \pm 1.9$   $t = 4.734$ ,  $P < 0.001$ ) and CRS (intervention  $13.4 \pm 10.1$  to  $12.4 \pm 10.5$ , control  $9.4 \pm 6.7$  to  $15.0 \pm 6.1$   $t = -2.537$ ,  $P < 0.05$ ). RPE rating decreased in intervention subjects ( $13.4 \pm 12.2$  to  $12.4 \pm 2.0$ ) and increased in controls ( $13.8 \pm 1.8$  to  $14.4 \pm 1.6$ ); Mann-Whitney *U* ( $U = 173.5$ ,  $P < 0.05$ ). Within-group comparison showed significant decrease in the HADS depression subscale in the intervention group alone ( $5.1 \pm 3.4$  to  $3.0 \pm 2.8$ ) (Wilcoxon signed ranks test  $Z = -3.278$ ,  $P < 0.001$ ).

**Conclusion:** Preliminary findings suggest non-acute ischaemic stroke patients can improve their cardiovascular fitness and reduce their CRS with a cardiac rehabilitation programme. The intervention was associated with improvement in self-reported depression.

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## Introduction

Cardiovascular disease and ischaemic stroke are both vascular diseases sharing many predisposing, potentially modifiable risk factors (hypertension, abnormal blood lipids and lipoproteins, cigarette smoking, physical inactivity, obesity and diabetes mellitus).<sup>1,2</sup> Their association is not benign, with the risk of death in the stroke population, in part due to cardiac disease, at least twice that of age-matched controls.<sup>3</sup> Modification of multiple risk factors through lifestyle interventions and pharmacological therapy is recognized as the cornerstone of prevention of recurrent events.<sup>3-5</sup>

Regular physical activity and cardiac rehabilitation have proven benefits in the general population and post cardiac event,<sup>6-9</sup> however, adoption of the cardiac rehabilitation paradigm to the ischaemic stroke population has remained untested. Stroke patients are known to have low endurance to exercise and decreased activity levels<sup>10</sup> and few can avail themselves of cardiovascular training through exercise counselling alone due to acquired disability.<sup>11</sup> A Cochrane review and the American Stroke Association have highlighted as a priority the need for research into the efficacy and feasibility of aerobic exercises post stroke.<sup>2,12</sup>

As adapted cycle ergometers allow aerobic fitness training post stroke<sup>10,13,14</sup> this pilot study aims to establish the feasibility of a 10-week cardiac rehabilitation programme including 16 cycle ergometry sessions. Of interest is whether the programme improves:

- Cardiovascular fitness using estimated  $\dot{V}O_2$  and Borg's Rate of Perceived Exertion<sup>15</sup> (RPE), at a given workload and resting heart rate (HR).
- Multivariate cardiac risk score<sup>16</sup> (CRS) measured by a coronary disease prediction algorithm.
- Cardiovascular-metabolic risk factor profile using fasting lipid profiles and resting blood pressure.
- Health-related function and quality of life as measured by the Frenchay Activity Index<sup>17</sup> and the Hospital Anxiety and Depression Scale.<sup>18</sup>

## Methods

### Study design

A randomized, controlled, single-blind trial was conducted, approved by University College Dublin Human Research Ethics Committee. Measurements were made by an independent assessor blinded to allocation.

### Patients

Subjects were recruited from the Stroke Rehabilitation Database, Baggot Street Community Hospital, Dublin. Information leaflets were posted and volunteers contacted the research team for initial telephone screening, including the PAR-Q Questionnaire.<sup>19</sup>

Informed consent was obtained. Participants' general practitioners were asked to notify contraindications to exercise or medication changes. All participants received a medical screening by a physician in the stroke unit prior to participation.

Sample size calculations with 80% power and  $P < 0.05$  were conducted on the following outcome measures:

- Borg's RPE<sup>15</sup> scale to detect a 2-point change between groups indicated that a minimum of 16 subjects would be required per group (mean 17 (SD 2)).<sup>20</sup>
- Hospital Anxiety and Depression Scale (HADS) depression subscale to detect a 2.5-point change between groups indicated a minimum of 24 per group (mean 6.2 (SD 3.1)).<sup>21</sup>
- Systolic blood pressure reduction of 5 mmHg indicated a minimum of 170 subjects in each group<sup>22</sup> which was not feasible for this pilot study. Data for CRS in stroke patients was not available for sample size calculation.

Inclusion criteria: >1 year post ischaemic stroke (confirmed by CT or MRI scan) and over 18 years of age. Patients were included irrespective of their ability to ambulate independently.

Exclusion criteria:  $O_2$  dependence, angina, unstable cardiac conditions, uncontrolled diabetes mellitus, major medical conditions, claudication, febrile illness, cognitive impairment or beta

blocker medication (RPE, a primary outcome measure, was shown to be unreliable in subjects taking beta blocker medication).<sup>22,23</sup>

### Random allocation

Participants were assigned an ID number, stratified by age and sex into four blocks of six and randomly assigned using a sequence generator (SPSS version 12.0), to either intervention or control groups, by an independent party. Following initial testing, participants were handed an opaque envelope which contained details of their group assignment, by clerical staff unrelated to the trial.

### Programme

Both control and intervention subjects who were in receipt of physiotherapy and occupational therapy services continued with usual care. Occupational and physiotherapy received focused on functional activities, balance and gait. No therapy contained an aerobic exercise component.

Control subjects had a baseline assessment on week 1 and re-assessment on week 10 with no additional intervention in the interim.

The Cardiac Rehabilitation Programme consisted of a 10-week schedule with baseline measures in week 1 and reassessment in week 10. Intervention subjects attended twice weekly for 30-minute cycle ergometry exercise (Motomed Viva 2) using either the upper or lower limbs. They exercised through biofeedback alarms set at 50–60% of their maximal heart rate, calculated sessionally (Karvonen formula  $THR = (HR_{max} - HR_{rest})(50-60\%) + HR_{rest}$ ). Resistance and speed were adjusted daily to ensure tailored progression. As participants did not exceed 60% max HR, the programme posed very low risk of adverse events.<sup>2</sup> Participants attended two life skills classes addressing stress management, relaxation and life balance.

Two participants exercised concurrently in a controlled environment and all sessions were supervised by a physiotherapist. Staff had cardiac resuscitation and defibrillation certification. Indications to stop exercise included: chest pain,

dizziness, malaise, heart rate in excess of 60% maximal heart rate, oxygen saturation levels lower than 90% or participant request to stop in accordance with American Heart Association (AHA) guidelines.<sup>24</sup>

### Measurements

- Baseline descriptives including Oxfordshire Stroke Subtype Classification,<sup>25</sup> medical history including stroke, previous cardiac events and Functional Ambulation Category<sup>26</sup> were noted from each participant's medical chart.
- Fitness testing<sup>19</sup> was conducted with a standardized 3-minute submaximal exercise test using a cycle ergometer (Reck, Motomed Viva 2) at resistance setting 8 (5.6 Nm). Participants were fasting overnight for 12 hours at the time of testing, they were instructed to wear loose, comfortable clothing and room temperature was maintained at 20°C. The machine passively moved for 1 minute at 50 rpm, allowing a warm-up and assuring no joint discomfort. Participants took over pedalling for 3 minutes at a steady state of 50 rpm with a workload of 5.6 Nm. A metronome was present to assist with pacing.
- $\dot{V}O_2$  (mL  $O_2$ /kg/min) was calculated  $(10.8 \times W \times M^{-1}) + 7$ , using average wattage output during the test.
- RPE was rated at the end of the test, in accordance with the recommended guidelines.<sup>15</sup>
- Peak wattage was recorded at the end of the 3-minute exercise test.
- Cardiac risk score<sup>16</sup> (CRS) was calculated for each participant. This is an algorithmic score based on age, resting blood pressure, smoking status, diabetic status, total cholesterol and high-density lipoprotein (HDL) scores.
- Resting heart rate and  $SaO_2$  were measured following a 5-minute seated rest period (Nanox 2 oximeter, Medlab).
- Resting brachial artery blood pressure (unaffected limb) was measured with a calibrated mercury sphygmomanometer in accordance with the Joint National Committee VI.<sup>27</sup>
- Body mass index (BMI) was calculated using a calibrated weighing scales and metre rule.

- Fasting lipids were measured from blood samples obtained by venipuncture following overnight fasting by the subjects. Serum was analysed for total cholesterol and triglycerides. HDL cholesterol was determined from plasma. Low-density lipoprotein (LDL) cholesterol calculated using the Friedewald equation.<sup>28</sup>
- Frenchay Activity Index<sup>17</sup> and HADS<sup>18</sup> forms were filled in by all participants.
- Spirometry testing was performed with the participant in upright sitting using the Microlab 3300 (Micro Medical Limited). Routine use of respiratory medications including inhalers was permitted.

#### Data analysis

Data were entered onto the Statistical Package for the Social Sciences (SPSS) version 12. Analysis performed was on an intention to treat basis and

as such final scores are included on patients who failed to complete the intervention.<sup>29</sup> Change scores were compared between groups using independent *t*-tests where data were interval or ratio level and conformed to the assumptions of normality. Mann-Whitney non-parametric tests were otherwise used. Ancillary analysis included single-group analysis using paired *t*-tests and Wilcoxon signed ranks test.

#### Results

Demographic and clinical characteristics of the intervention and control groups are presented in Table 1. Forty-eight subjects entered the trial with participant flow represented in Figure 1.

No change in cholesterol lowering medication was reported in either group. Three control subjects had blood pressure medication changes during the trial: subject 4, from hypertension

**Table 1** Baseline and clinical descriptives

Baseline descriptives	Control (n = 24) Mean (SD)	Active (n = 24) Mean (SD)
Age (years)	60.5 (10.0)	59.0 (10.3)
Time since cerebrovascular accident (CVA) (weeks)	245.3 (169.8)	237.3 (110.7)
	n (%)	n (%)
Male	14 (58%)	14 (58%)
Female	10 (42%)	10 (42%)
Right CVA	11 (45%)	13 (54%)
Left CVA	13 (54%)	11 (45%)
Oxfordshire Stroke Subtype Classification		
Total anterior circulation infarct (TACI)	1 (4.2%)	3 (12.5%)
Partial anterior circulation infarct (PACI)	12 (50%)	9 (37.5%)
Lacunar infarct (LACI)	5 (20.8%)	7 (29.2%)
Posterior circulation infarct (POCI)	3 (12.5%)	2 (8.3%)
Unknown	3 (12.5%)	3 (12.5%)
Functional Ambulation Category		
0	1 (4.2%)	0 (0%)
1	2 (8.3%)	3 (12.5%)
2	1 (4.2%)	1 (4.2%)
3	1 (4.2%)	1 (4.2%)
4	6 (25%)	4 (16.7%)
5	13 (54.2%)	15 (62.5%)
Known cardiac history		
Ischaemic heart disease	1 (4.2%)	3 (12.5%)
Myocardial infarct	1 (4.2%)	0 (0%)
Coronary artery bypass graft	0 (0%)	1 (4.2%)
Atrial fibrillation	2 (8.3%)	2 (8.3%)
Recurrent stroke	3 (12.5%)	4 (16.7%)

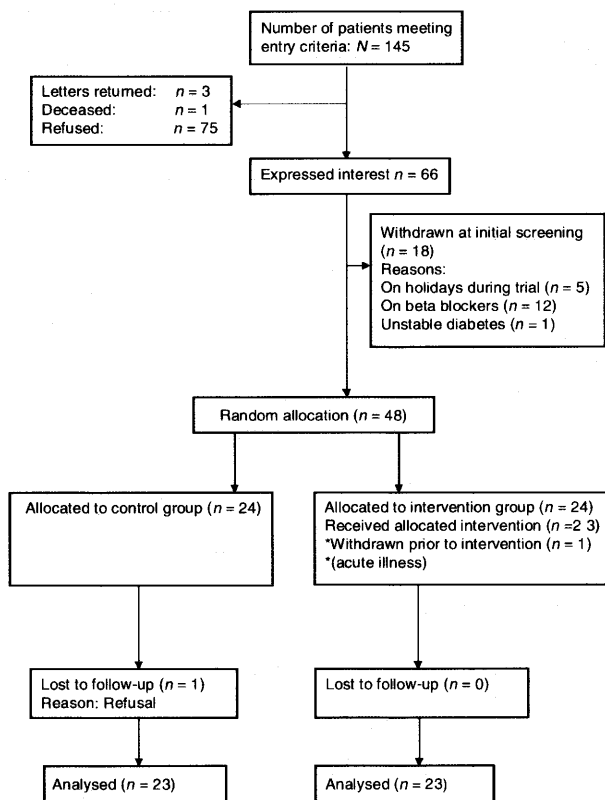


Figure 1 Participant flow diagram.

monotherapy to angiotensin II antagonist/thiazide, subject 12 was prescribed a diuretic tablet the day before retesting and subject 34 had hypertension medication increased. Of the intervention group no change to hypertension agents was noted. Seven of the 48 subjects recruited to the study (3 control, 4 intervention) continued usual therapy as described in the programme outline.

Table 2 illustrates control and intervention group scores demonstrated at baseline and follow-up. Baseline scores were compared between groups with no significant differences noted, despite outliers in BMI and time since stroke in the intervention and control groups, respectively. Outliers were included in analysis. Between-sex differences were noted in baseline data with males scoring significantly higher on forced expiratory volume in 1 second (FEV<sub>1</sub>) ( $P=0.005$ ), peak wattage ( $P<0.001$ ) and total cholesterol ( $P=0.02$ ).

When change scores were compared between groups, the intervention arm demonstrated significantly greater improvements after treatment in several primary variables when compared with the control. Overall cardiovascular fitness improved in the intervention group with greater increase in  $\dot{V}O_2$  ( $t\ 4.734$ ,  $P<0.001$ ) and decrease in RPE ( $U\ 173.5$ ,  $P=0.04$ ) by comparison with the controls. Cardiac risk score reduced in the intervention group but increased in the controls ( $t\ -2.537$ ,  $P=0.015$ ). No significant change occurred in cardiovascular-metabolic risk factor profiles of total cholesterol, LDL, HDL, triglycerides, systolic and diastolic blood pressures. Similarly, no significant difference was found in the Frenchay Activity Index or HADS change scores.

Secondary outcome analysis demonstrated no significant difference in change scores between groups in spirometry results of forced vital capacity (FVC), peak expiratory flow (PEF), FEV<sub>1</sub> and FEV<sub>1</sub>/FVC (%). Peak wattage output reflecting peak power generated by the limbs during testing increased in the intervention group compared to the control ( $t\ 4.035$ ,  $P<0.001$ ).

When within-group analysis was performed using paired  $t$ -tests and Wilcoxon signed ranks test where appropriate, only the intervention group had a significant change in  $\dot{V}O_2$  ( $P<0.001$ ) and cardiac risk score ( $P=0.005$ ). It is interesting to note that the HADS depression score also improved significantly in the intervention group ( $Z\ -3.278$ ,  $P<0.001$ ), but not in the control. BMI increased in both control ( $P=0.008$ ) and intervention ( $P=0.012$ ) groups.

Between-sex comparison of change scores in the intervention arm indicates both males and females benefited equally from the intervention (no significant differences noted).

## Discussion

This pilot randomized controlled trial study tested the feasibility of a 10-week cardiac rehabilitation programme, demonstrating its efficacy with significant increases in fitness parameters of  $\dot{V}O_2$  and RPE and cardiac risk score reduction in the intervention group.

**Table 2** Pre- and post-treatment scores for control and active groups

	Control (n=23)			Active (n=23)			Analysis of between-group change		
	Pre	Post	Change	Pre	Post	Change	P-value	95% CI	Effect size
<b>Cardiac risk</b>									
Waist girth (mm × 10 <sup>2</sup> )	96.5 ± 10.8	97.5 ± 11.0	1.0	103.0 ± 12.4	103.0 ± 15.7	-0.1	0.602	-5.2, 3.0	
Total cholesterol (mmol/L)	4.6 ± 1.2	4.7 ± 1.1	0.1	4.6 ± 1.1	4.5 ± 1.0	-0.1	0.192	-0.4, 0.1	
Cardiac risk score	9.4 ± 6.8	10.4 ± 6.1	1.0	12.0 ± 10.3	10.4 ± 10.5	-1.5*	0.015	-4.4, -0.5	0.8
Resting systolic BP (mmHg)	135.2 ± 17.5	133.5 ± 16.7	-1.7	137.1 ± 15.7	136.0 ± 13.3	-1.1	0.903	-8.7, 9.8	
Resting diastolic BP (mmHg)	81.8 ± 11.6	82.0 ± 9.0	0.2	79.7 ± 7.6	81.4 ± 8.4	1.7	0.545	-3.7, 6.9	
<b>Fitness and function</b>									
Body mass index (kg/m <sup>2</sup> )	25.7 ± 3.7	26.2 ± 3.7	0.5*	28.1 ± 5.6	28.7 ± 5.5	0.6*	0.604	-0.4, 0.7	
Resting HR (bpm)	70.1 ± 10.2	70.9 ± 11.3	0.8	72.3 ± 10.2	72.9 ± 10.9	0.6	0.948	-7.2, 6.7	
FEV <sub>1</sub> (L)	1.9 ± 0.8	1.9 ± 0.7	0.0	2.3 ± 0.8	2.2 ± 0.8	-0.1	0.778	-0.2, 0.2	
VO <sub>2</sub> (mL O <sub>2</sub> /kg/min)	11.1 ± 1.8	11.1 ± 1.9	0.0	10.6 ± 1.6	12.0 ± 2.2	1.4*	<0.001	0.8, 2.1	1.3
Peak wattage (Nm)	57.4 ± 29.1	56.3 ± 30.2	-1.1	56.6 ± 31.8	75.3 ± 39.2	18.7*	<0.001	9.9, 30.0	1.4
Rate of perceived exertion, median (range)	14.0 (9-16)	15.0 (11-17)	1.0 (-2-5)	13.0 (9-17)	13.0 (7-17)	-1 (-7-4)	0.043		
<b>Self-reported function and HROoL</b>									
HADS									
Anxiety, median (range)	7.0 (1-13)	6.0 (0-18)	-1.0 (-8-5)	5.0 (0-11)	4.0 (0-16)	-1.0 (-5-13)	0.938		
Depression, median (range)	6.0 (0-20)	4.0 (1-20)	-1.0 (-6-3)	4.0 (0-13)	2.0 (0-11)	-1.0 (-11-2)†	0.222		
Frenchay Activity Index, median (range)	26.0 (7-42)	27.0 (3-40)	1.0 (-7-11)	26.0 (3-42)	27.0 (8-42)	1.0 (-7-11)	0.724		

\*Paired t-test for within-group differences.

†Wilcoxon sign rank test for within-group differences.

Active group: Cardiac risk score (P=0.005); BMI (P=0.012); VO<sub>2</sub> (P<0.001); peak wattage (P=0.001); HADS depression subscale (P=0.001).

Control group: BMI (P=0.008).

CI, confidence interval; BP, blood pressure; HR, heart rate; FEV<sub>1</sub>, forced expiratory volume in 1 second; HROoL, health-related quality of life; HADS, Hospital Anxiety and Depression Scale.

No significant improvements were noted in health-related quality of life (HRQoL) indices or cardiovascular-metabolic profiles. Decreased HADS depression scores on final testing in the active group does however suggest an associated increase in well-being. As a pilot study with relatively small numbers, limited power to demonstrate health status and functional benefits exists.

Another limitation of the methodology employed in this study is that the control group did not receive comparable non-exercise related attention to the intervention group. Thus there may be a potential Hawthorn effect.

The Cochrane Review on Physical Fitness Training in Stroke Patients<sup>12</sup> details only two studies including measures of aerobic fitness ( $\dot{V}O_2$ ) and maximal work rate (Watts)<sup>10,30</sup> and two meeting the American College of Sports Medicine (ACSM) guidelines for developing cardiorespiratory fitness.<sup>10,31</sup> This study complies with cardiovascular training requirements by the rigour of the training programme described and similar improvements in fitness parameters  $\dot{V}O_2$  and RPE were observed in this study. As no aerobic training component was included in usual therapy, common to both groups, these changes may be attributed to the intervention. It has been demonstrated in the literature that stroke patients can improve their fitness levels to the same degree as their age-matched counterparts.<sup>10</sup> This study, through deployment of the CRS outcome measure, demonstrates the benefit of such interventions on vascular risk reduction.

Previous studies noted that improvement in RPE and  $\dot{V}O_2$  cannot distinguish between central and peripheral adaptation.<sup>10,32</sup> This was also observed in this study with a significant increase in peak wattage in the intervention group compared to the control, indicating that a lower limb muscle training effect must be considered as well as central cardiac adaptation to the exercise programme.

Comparison with cardiac rehabilitation programmes for the coronary heart disease populations is limited as primary outcome measures of mortality and non-fatal cardiac events were not feasible in the short time-frame and limited subject numbers in this pilot study. However, meta-analysis of exercise-based

rehabilitation in coronary heart disease<sup>8</sup> has demonstrated a net reduction in total cholesterol and LDL in comprehensive cardiac rehabilitation groups but not in exercise-only interventions. As both groups in this study demonstrated no significant change in lipoprotein profiles and increases in BMI over the trial period, it suggests future interventions should involve dietary education.

Two coronary heart disease trials<sup>33,34</sup> noted favourable decreases in both systolic and diastolic blood pressure in comprehensive cardiac programmes. However, systematic review noted an increase in blood pressure over trial periods in both groups in a number of studies.<sup>8</sup> As increases were more marked in the control groups, the net changes were considered negative. This study demonstrated a drop in systolic blood pressure in both groups and an increase in diastolic blood pressure in both groups. A number of subjects in the control group had a change in hypertension medications over the course of the trial but no change in medication noted in the intervention group, suggesting a possible trend toward blood pressure reduction in the intervention group.

Higher cardiac risk scores in the intervention group occurred because, despite randomization, the intervention arm contained three more people with diabetes than the control. This status does not change from initial to final testing. Similarly both groups contained six smokers and 17 non-smokers, with smoking status remaining unchanged on final testing. Therefore the cardiac risk reduction scores were as a result of alteration of resting blood pressure and fasting cholesterol measurements. While no significant change was seen in either variable in isolation, when considered in the context of a weighted algorithmic score, cardiac risk scores were reduced in the intervention group. Given the absence of change in cholesterol lowering medications in both groups and pharmacological management of hypertension in the intervention group, this may be attributed to the programme.

The authors acknowledge the cardiac risk score algorithm used is not validated for non-caucasians (subject 1; intervention group) and those over 74 years old (subject 13; control and subject 19; intervention). Analysis of cardiac risk change

scores with these subjects' data removed however, continues to demonstrate significantly greater cardiac risk reduction in the intervention group ( $t -2.512$ ,  $P=0.016$ ).

Modification of all major cardiovascular risk factors, including physical inactivity, is reported to be cost-effective but needs to be better targeted for potential health gain.<sup>35</sup>

No study to date has looked at reducing vascular risk profiles in ischaemic stroke through adoption of the cardiac rehabilitation paradigm. These findings show promise for such programmes as preventative interventions for further stroke and cardiac events. Using baseline data from this study, sample size estimation ( $n > 2K\sigma^2/\Delta^2$  ( $K=7.8$ )) suggests a minimum of 120 subjects in each group would be required to show expected change in all primary outcome measures in a definitive study, to be conducted by this research group.

#### Clinical messages

- Ischaemic stroke patients have high risk of coronary heart disease and recurrent stroke.
- Stroke patients are known to have low exercise endurance.
- Submaximal aerobic training is both safe and feasible in chronic stroke using adapted cycle ergometry.
- The cardiac rehabilitation paradigm adapted to stroke reduces cardiac risk and increases aerobic fitness in chronic ischaemic stroke patients.

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