Cardiovascular Fitness Training for a Patient in the Early Stages of Recovery Post Stroke

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INTRODUCTION

Over the past decade cardiovascular (CV) fitness training has begun to be incorporated as a standard component of stroke rehabilitation. With any change in practice, clinicians are interested in the best available evidence to guide safe and effective application of the novel intervention. This evidence-based article uses a real-life case to address issues commonly encountered in prescribing CV training for patients in the early post-stroke period.

CLINICAL QUESTION

What is the evidence regarding CV fitness training for a person early post stroke in terms of (1) rationale for use of CV training, (2) expected outcomes (effectiveness), and (3) prescription?

Clinical Case

J.M. is a 55-year-old forklift operator with a Grade 12 education who lives alone in a suburban trailer park. He is a non-smoker who does not exercise regularly outside of work but enjoys fishing and the occasional game of golf. He was found alone in his home with right-sided weakness and mild expressive aphasia. Computerized axial tomography revealed an infarct in the left basal ganglia, electroencephalography showed epileptiform activity, and carotid doppler demonstrated moderate plaque within carotid bulbs and 50% stenosis in the left internal carotid artery. Two years before this incident, J.M. had been diagnosed with paroxysmal non-valvular atrial fibrillation (NVAf), and 6 months prior to this incident he had experienced a transient ischemic attack (TIA) with right-sided weakness.

After a 9-day admission to the acute stroke centre, J.M. was transferred to a rehabilitation centre. Currently he is on phenytoin (Dilantin, 100 mg, 4×/day, to control

seizure activity), metoprolol (Lopressor, 200 mg, 1×/day, to reduce blood pressure [BP] and control NVAf), and atorvastatin (Lipitor, 40 mg 1×/day, to normalize his lipid profile). His body mass index (BMI) is 29.6 kg/m² and his waist circumference is 112 cm. Impairment-level findings on assessment included mild cognitive impairment (MCI; Montreal Cognitive Assessment 25/30); hypertonia in the left plantarflexors (1+ on the Modified Ashworth Scale [MAS]); reduced motor control of the left upper and lower extremities (Chedoke–McMaster Stages of Recovery: Arm = 2, Hand = 1, Leg = 5, Foot = 4); and impaired postural control (45/56 on the Berg Balance Scale [BBS]). Activity-level findings included impaired mobility (locomotor FIM = 6, *independent with an ambulatory aid—single cane*; 10 m gait speed of 64 cm/sec) and low walking endurance (6-minute walk test [6MWT] = 235 m with two standing rests; post-6MWT rating of perceived exertion [RPE_{0–10}] = 6; change in BP from 136/85 at rest to 172/90 post 6MWT).

THE EVIDENCE

Rationale for Prescribing CV Fitness Training for J.M.

To determine whether CV fitness training is appropriate for J.M., we begin by considering potential contraindications based on his current *health condition*. J.M. is in the early phase of recovery from a subcortical stroke. Safe and effective participation in aerobic exercise as early as 8 days post stroke has been reported in a small clinical trial.¹ That J.M. has diagnosed seizure activity is not an absolute contraindication to fitness training; while the relationship between epilepsy and exercise remains the subject of controversy, reduced incidence of seizures while exercising has been well documented.^{2,3} Thus, provided that J.M. is compliant with his anticonvulsant medication, it appears that the potential benefits of CV training outweigh the risk. J.M.

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has also been diagnosed with NVAf, which is an independent risk factor for stroke⁴ and sometimes (as in J.M.'s case) coexists with carotid stenosis.⁵ Although NVAf can adversely affect exercise performance, it does not negate the beneficial effects of CV training.⁶ Further, J.M. has paroxysmal (as opposed to persistent) NVAf, which is controlled by medication. For these reasons, the cardiologist involved in J.M.'s case did not consider NVAf a contraindication to exercise. Similarly, the extent of narrowing of J.M.'s left internal carotid artery (50%) falls at the upper end of mild stenosis, and therefore physical activity is not contraindicated.⁷

It is highly likely that J.M. has metabolic syndrome (MetS)—a constellation of metabolic abnormalities that interact to accelerate the progression of atherosclerosis and increase the individual's risk of developing vascular disease involving the heart, the brain, or both.⁸ MetS, present in about 60% of stroke rehabilitation participants,⁹ is predictive of stroke recurrence.¹⁰ Components of MetS (as defined by the International Diabetes Federation¹¹) manifested by J.M. include abdominal obesity (waist circumference >94 cm for males), diagnosed hypertension (systolic BP $\geq$ 130 mm Hg or diastolic BP $\geq$ 85 mm Hg), and dyslipidemia. This clustering of metabolic abnormalities is associated with low exercise capacity.¹² Moreover, people with cardiovascular disease who have MetS but not diabetes have a 1.5-fold increased risk of ischemic stroke or TIA.¹³ Aerobic training, especially of moderate intensity,¹⁴ can modify all components of MetS.^{15,16}

In terms of *personal contextual factors*, although J.M. is 16 years younger than the reported mean age of male Canadians at the time of stroke, physiologically he would be classified as an "older individual" because of his physical limitations.¹⁷ Nevertheless, Kohrt et al.¹⁸ have demonstrated that trainability is not influenced by age or gender, at least in non-disabled adult populations. J.M.'s low pre-morbid level of physical activity is predictive of a poorer long-term outcome post-stroke.¹⁹

The *impairment-level finding* of plantarflexor spasticity does not contraindicate aerobic exercise post stroke.^{20–22} The finding of minimal cognitive impairment (MCI) is a possible indication for prescription of fitness training, given extensive evidence of exercise-induced improvements in executive function of non-disabled older adults²³ and preliminary evidence of enhanced procedural motor learning, but not executive function, in people with remote stroke (i.e., >6 months post).²⁴ Improved cognition may be due in part to increased cerebral blood flow in the hippocampus, which in turn may be due to up-regulation of brain-derived neurotrophic factor, a key mediator in synaptic plasticity.²⁵ However, a recent study reported that only women with MCI improved executive function via aerobic exercise,²⁶ which suggests that this benefit may not be realized by J.M.

In terms of *activity-level findings*, J.M.'s comfortable walking speed is about 46% of predicted,²⁷ and his predicted ambulatory status would be "least-limited community ambulator."²⁸ During the 6MWT he walked ~40% of the predicted distance for his age and stature,²⁹ required rest breaks, had a hypertensive response, and reported an RPE_{0–10} between 5 ("hard") and 7 ("very hard"). Although self-selected walking speed and 6MWT distance are not highly correlated with maximal oxygen capacity after stroke,^{30,31} J.M.'s slow walking speed and poor performance on the 6MWT are indicative of low exercise tolerance, which can be enhanced through training, as discussed in the next section.

In summary, several features of J.M.'s clinical presentation suggest that he is deconditioned and in poor vascular health. Despite the fact that J.M. is in the early post-stroke phase and has several comorbidities, the evidence supports the decision to engage him in CV fitness training.

Expected Outcomes of a CV Fitness Programme for J.M.

Assuming that J.M. undergoes CV fitness training, what aspects of his presentation can be expected to change as a result of training, and to what extent, based on the stroke-specific literature? The effects of aerobic exercise on *CV risk factors* for further vascular morbidity have not been well studied. Two training studies of people with remote stroke, which involved 10 weeks of cycle ergometry³² and 14 weeks of cycle ergometry and stepper training,³³ reported mean reductions in resting systolic BP of 7.1 and 10.3 mm Hg, respectively. If J.M. were to attain that level of BP reduction, he would no longer be considered hypertensive. In addition to a BP-lowering effect, the latter study also reported a 27% reduction in triglycerides and a 9% decrease in total cholesterol.³³ Interestingly, training did not elicit a change in high-density lipoprotein cholesterol (HDL-C), the form of cholesterol shown to be most positively affected by aerobic exercise in non-stroke populations.³⁴

In another study, a 6-month treadmill exercise programme for patients with remote stroke led to 23% mean reductions in fasting plasma glucose and a 14% decrease in 3-hour glucose response.³⁵ The investigators concluded that progressive aerobic exercise following stroke may reduce insulin resistance and prevent diabetes.³⁵ Because J.M. is at risk of becoming diabetic, this potential benefit is significant. Whereas body weight and fat-free body mass did not change in the latter study,³⁵ Rimmer et al. found a small, but significant, mean decrease in BMI of 0.33 kg/m² following a 12-week multimodal exercise program.³⁶ Another pilot randomized controlled trial (RCT) of a 10-week cardiac rehabilitation programme for people with remote stroke demonstrated a 13% reduction in composite cardiac risk score in the experimental group versus an 11% increase in the usual

care group.³⁷ No changes in waist circumference, resting BP, or total cholesterol were found in either group.³⁷

The evidence from the literature is clear that stroke survivors in both early and later stages of recovery can improve their *exercise capacity* through progressive aerobic exercise. The extent of change in peak oxygen uptake ($\dot{V}O_2$) varies depending on patient characteristics (e.g., severity of stroke, time post stroke), programme parameters (e.g., intensity of training, duration of program, frequency of sessions), and nature of the study (e.g., RCT, cohort study). In the two trials that examined patients <6 months post stroke (and therefore are most applicable to J.M.) and that measured exercise capacity, mean peak $\dot{V}O_2$ increases were 9% (1.0 mL/kg/min; 0.3 metabolic equivalent [MET], RCT)³⁸ and 13% (1.5 mL/kg/min; 0.4 MET, cohort study).³⁹ To put these findings in context, an improvement of 1 MET has been associated with a 12% increase in survival among men with cardiac disease.⁴⁰

An important clinical question to ask is, *Do aerobic-training-induced gains in exercise capacity post stroke translate into functional improvements?* Unfortunately, the evidence here is limited. RCTs involving patients <6 months post stroke have demonstrated mean increases in comfortable *walking speed* that were inversely related to the baseline speed (i.e., the lower the initial speed, the greater the percentage of improvement).^{38,39,41,42} Average improvements ranged from 26% (0.18 m/sec change, from 0.70 m/sec at baseline to 0.88 m/sec after training)³⁸ to 238% (0.31 m/sec change, from 0.13 to 0.44 m/sec).⁴² In all the trials, the average improvement in gait speed exceeded the minimal clinically important difference (MCID) of 0.16 m/sec for patients in the subacute stage of recovery after stroke.⁴³ Increasing J.M.'s walking speed by the MCID would yield a speed of 0.83 m/sec, which would elevate his predicted ambulatory status to "community ambulator."²⁸

There is also evidence of clinically meaningful improvement in *walking endurance* in response to CV training early after stroke. Several studies have found that extent of change in 6MWT distance following training was inversely related to the baseline distance, with mean changes ranging from 26% (62 m change, from 238 m at baseline to 300 m after training)³⁸ through 53% (123 m change, from 207 to 330 m)³⁹ and 84% (91 m change, from 108 to 199 m)⁴¹ to 319% (102 m, from 32 to 134 m).⁴² Again, the mean change in 6MWT distance in each study exceeded the minimal detectable change (MDC) of 54 m in people with stroke undergoing inpatient rehabilitation.⁴⁴ Nevertheless, the post-training 6MWT distance attained in these training studies did not exceed 350 m, the approximate distance needed for community functioning; 6MWT distances <350 m are associated with a substantial increase in risk of mortality.⁴⁵ Based on the evidence, it would be reasonable to expect that, with CV training, J.M. could attain

the MDC for the 6MWT (i.e., a post-training distance of ~289 m, or a 23% increase), but it is less plausible that he could reach the distance required for community ambulation (i.e., a post-training distance of 350 m, or a 49% increase).

Improvements in both metabolic and mechanical efficiencies are likely to underlie the anticipated training-induced increases in J.M.'s walking speed and endurance. Clearly, CV fitness training will enhance metabolic efficiency; however, training can also lead to improved neuromuscular control, resulting in greater mechanical efficiency. This effect is due in part to increased activation of hemiparetic lower-extremity muscles. In addition, the repetitive nature of aerobic exercise has been shown to trigger plasticity of the central nervous system and enhanced synaptic efficiency in brain networks that control the hemiparetic limb.⁴⁶ Indeed, using functional magnetic resonance imaging, Luft et al.⁴⁷ demonstrated increased activity in the cerebellum and brainstem during movement of the hemiparetic knee following a 6-month programme of aerobic treadmill training.

The above-mentioned benefits of CV training in the early post-stroke period (improved exercise capacity, walking speed, and walking endurance) suggest the possibility of concurrent improvements in *activities of daily living and independent living*. Unfortunately, evidence is lacking as to the effects of aerobic exercise programmes on activities of daily living and quality of life.⁴⁶ An RCT investigating the effects of an 8-week programme of cycle-ergometry training did not reveal change at the level of physical activity and social functioning for people with remote stroke.⁴⁸

It could be argued that devoting a portion of time-limited therapy sessions to CV training post-stroke might reduce functional recovery in other domains, such as *postural control*. The only CV training study to monitor change in postural control in patients <6 months post-stroke reported mean increases in the BBS of 10% in the CV training group and 4% in the usual care group.³⁸ Further, frequency of *adverse events* is an important consideration with respect to any therapeutic intervention. The most direct evidence here comes from a home-based study by Duncan et al., in which three people in the training group (9%) and no people in the usual care group (0%) sustained a second stroke during the trial.³⁸ The investigators concluded that since this incidence was consistent with the rate of recurrent stroke in the early post-stroke period, it should not preclude CV training, provided that supervision is adequate.³⁸

Prescription of CV Exercise for J.M.

The most effective *time post stroke to initiate training* has not been determined. Early initiation of stroke rehabilitation has in general been reported to be associated

with greater functional recovery that is sustained at 1-year follow-up,⁴⁹ an effect that has been attributed, in part, to enhanced neuroplasticity in the early post-stroke period.⁵⁰ However, whether this advantage applies to aerobic training per se has not been ascertained.

To guide the prescription of J.M.'s CV training programme, we reviewed exercise parameters used in training studies, with a particular focus on studies involving people <6 months post stroke. In terms of *format of the programme*, patients were trained individually, rather than in groups, in all of these studies; evidence of effective group training is limited to patients with remote stroke.^{51–54} The *total volume of training* averaged ~400 minutes (6.7 hours) in two studies^{39,42} and 900 minutes (15 hours) in two studies.^{38,41} *Program duration* ranged from ~4 weeks^{39,42} through 6 weeks⁴¹ to 12 weeks;³⁸ *frequency of exercise sessions* from 3^{38,39} to 5 days per week;^{41,42} and *session duration* from 20 minutes⁴² through 20–30 minutes³⁸ to 30 minutes.^{39,41} Very deconditioned stroke survivors may benefit from a discontinuous training protocol consisting initially of 2- to 5-minute bouts of exercise with rest intervals of similar duration.^{38,55} A meta-analysis of 25 non-stroke exercise trials (averaging 22.4 weeks in duration, 3.7 sessions/week, and 40.5 minutes/session) concluded that session duration was the most important element of aerobic exercise prescription for increasing HDL-C.⁵⁶

Mode of training also varied in the stroke trials. Cycle ergometry was used in the two studies of participants whose baseline walking status most closely resembled J.M.'s;^{38,39} the other two studies involved lower-functioning patients and used body-weight-supported (BWS) treadmill walking⁴¹ and electromechanical gait training consisting of two driven footplates simulating the gait cycle.⁴²

Determining an appropriate *training intensity* is one of the most important and most difficult challenges. In some of the above-mentioned training studies, target heart rate was calculated using the Karvonen formula: (training heart rate = resting heart rate + $x\%$ Heart Rate Reserve [HRR]), where HRR = maximal heart rate – resting heart rate.¹⁷ Since maximal heart rate is usually not measured directly in clinical practice, it can be estimated using various formulae—for example, predicted maximal heart rate = $206.9 - (0.67 \times \text{age})$.¹⁷ Because of the heart-rate-lowering effect of beta-adrenergic blocking agents, another formula is recommended for J.M.: predicted maximal heart rate = $164 - 0.7 \times \text{age}$.⁵⁷ One study set a target intensity of 60% HRR,⁴¹ while another used 50%–70% of the work rate achieved at peak $\dot{V}O_2$.³⁹ Ivey et al. have demonstrated that training people with remote stroke at 60–70% HRR, using three 40-minute sessions per week for 6 months, was effective in reducing insulin resistance.³⁵ A meta-analysis of nine aerobic exercise studies post stroke (mainly remote stroke) revealed that training

intensities of 50–80% HRR, sustained for 20–40 minutes per session and repeated 3–5 days per week, were effective in increasing exercise capacity.⁵⁸ In addition, Macko et al. reported that progressing treadmill speed (i.e., intensity) was more effective than increasing session duration for optimizing CV fitness in people with remote stroke.⁵⁹

In summary, although the optimal training protocol for J.M. cannot be derived from the literature, published protocols (particularly those involving patients <6 months post stroke) can help to inform an effective intervention strategy for J.M. Since J.M. is an in-patient, fitness training could be implemented 5 days/week in two to three 5-minute bouts, with 50% HRR as a target. Given J.M.'s levels of postural and motor control, several exercise modes could be considered: cycle ergometry, low BWS treadmill training (<20% BWS), or stepping. Heart rate should be monitored continuously, and BP checked at rest and at the end of each bout to monitor J.M.'s response to exercise. The exercise intensity should be progressed to 60–70% HRR, as tolerated, and the length of bouts should gradually be increased until a single continuous bout of 30–40 minutes is attained, if tolerated and feasible. Initially, J.M. should participate in individual, structured training sessions to ensure safety and effectiveness. Education on medication adherence and non-pharmacological approaches to CV risk-factor reduction and secondary stroke prevention is also important for J.M.'s self-management and long-term health status. To help with the transition to the community, he should be assisted in establishing a more independent CV training regimen that meets both the therapeutic objectives and his personal goals. Evidence suggests that self-efficacy and outcome expectations are important factors predicting engagement in physical activity following stroke;⁶⁰ what J.M. does for himself has greater potential for success than anything that can be prescribed for him.¹⁹

LIMITATIONS AND FUTURE RESEARCH

In the past 15 years, substantial progress has been made in clinical research on the effective application of aerobic exercise post stroke. Nevertheless, numerous gaps remain, including early post-stroke management; identification of effective training protocols based on the individual patient's baseline status (i.e., intervention algorithms); strategies to better engage patients in aerobic exercise; potency of training in improving function and quality of life; identification of CV risk factor and prevention of secondary stroke; and adaptation of fitness regimens to ensure sustainability across the continuum of care (i.e., from in-patients to outpatients to home and the community). Each of these gaps warrants further investigation.

REFERENCES

- da Cunha Filho IT, Lim PA, Quershy H, Henson H, Monga TN, Protas EJ. A comparison of regular rehabilitation and regular rehabilitation with supported treadmill ambulation training for acute stroke patients. *J Rehabil Res Dev*. 2001;38:245–55.
- Arida RM, Cavalheiro EA, da Silva AC, Scorza FA. Physical activity and epilepsy: proven and predicted benefits. *Sport Med*. 2008;38:607–15. doi:10.2165/00007256-200838070-00006
- Cantu R. Epilepsy and athletics. *Clin Sport Med*. 1998;17:61–9. doi:10.1016/S0278-5919(05)70061-2
- Hart RG, Halperin JL. Atrial fibrillation thromboembolism: a decade of progress in stroke prevention. *Ann Intern Med*. 1999;131:688–95.
- Benbir G, Uluduz D, Ince B, Bozulolcay M. Atherothrombotic ischemic stroke in patients with atrial fibrillation. *Clin Neurol Neurosurg*. 2007;109:485–90. doi:10.1016/j.clineuro.2007.03.009
- Vanhees L, Schepers D, Defoor J, Brusselle S, Tchursh N, Fagard R. Exercise performance and training in cardiac patients with atrial fibrillation. *J Cardiopulm Rehabil*. 2000;20:346–52. doi:10.1097/00008483-200011000-00003
- Sacco R. Extracranial carotid stenosis. *New Engl J Med*. 2001;345:1113–8. doi:10.1056/NEJMcp011227
- Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, et al. Metabolic syndrome and the risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol*. 2007;49:403–24. doi:10.1016/j.jacc.2006.09.032
- MacKay-Lyons M, MacDonald C, Howlett J. Metabolic syndrome and its components in individuals undergoing rehabilitation after stroke. *J Neurol Phys Ther*. 2009;33:189–94.
- Liou CW, Tan TY, Lin TK, Wang PW, Yip HK. Metabolic syndrome and three of its components as risk factors for recurrent ischaemic stroke presenting as large-vessel infarction. *Eur J Neurol*. 2008;15:802–9. doi:10.1111/j.1468-1331.2008.02181.x
- Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition: a consensus statement from the International Diabetes Federation. *Diabetic Med*. 2006;23:469–80. doi:10.1111/j.1464-5491.2006.01858.x
- LaMonte MJ, Barlow CE, Jurca R, Kampert JB, Church TS, Blair SN. Cardiorespiratory fitness is inversely associated with the incidence of metabolic syndrome: a prospective study of men and women. *Circulation*. 2005;112:505–12. doi:10.1016/j.accreview.2005.10.021
- Koren-Morag N, Goldbourt U, Tanne D. Relation between the metabolic syndrome and ischemic stroke or transient ischemic attack: a prospective cohort study in patients with atherosclerotic cardiovascular disease. *Stroke*. 2005;36:1366–71. doi:10.1161/01.STR.0000169945.75911.33
- Johnson JL, Slentz CA, Houmard JA, Samsa GP, Duscha BD, Aiken LB, et al. Exercise training amount and intensity effects on metabolic syndrome (from studies of a targeted risk reduction intervention through defined exercise). *Am J Cardiol*. 2007;100:1756–66. doi:10.1016/j.amjcard.2007.07.027
- Gayda M, Brun C, Juneau M, Levesque S, Nigam A. Long-term cardiac rehabilitation and exercise training programs improve metabolic parameters in metabolic syndrome patients with and without coronary heart disease. *Nutr Metab Cardiovasc*. 2008;18:142–51. doi:10.1016/j.numecd.2006.07.003
- Mohan V, Gokulakrishnan K, Deepa R, Shanthirani CS, Datta M. Association of physical inactivity with components of metabolic syndrome and coronary artery disease—the Chennai Urban Population Study (CUPS no. 15). *Diabetic Med*. 2005;22:1206–11. doi:10.1111/j.1464-5491.2005.01616.x
- American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2010.
- Kohrt WM, Malley MT, Coggan AR, Spina RJ, Ogawa T, Ehsani AA, et al. Effects of gender, age, and fitness level on response of VO_2max to training in 60–71 yr olds. *J Appl Physiol*. 1991;71:2004–11.
- Krurup LH, Truelsen T, Gluud C, Andersen G, Zeng X, Korv J, et al. Prestroke physical activity is associated with severity and long-term outcome from first-ever stroke. *Neurology*. 2008;71:1313–8. doi:10.1212/01.wnl.0000327667.48013.9f
- Saunders DH, Greig CA, Mead GE, Young A. Physical fitness training for stroke patients. *Cochrane Db Syst Rev*;2009:4. doi:10.1002/14651858.CD003316.pub3
- Smith GV, Silver KHC, Goldberg AP, Macko RF. “Task-oriented” exercise improves hamstring strength and spastic reflexes in chronic stroke patients. *Stroke*. 1999;30:2112–8.
- Teixeira-Salmela LF, Olney SJ, Nadeau S, Brouwer B. Muscle strengthening and physical conditioning to reduce impairment and disability in chronic stroke survivors. *Arch Phys Med Rehabil*. 1999;80:1211–8. doi:10.1016/S0003-9993(99)90018-7
- Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci*. 2003;14:125–30. doi:10.1111/1467-9280.t01-1-01430
- Quaney B, Boyd LA, McDowd JM, Zahner LH, He J, Mayo S, et al. Aerobic exercise improves cognition and motor function poststroke. *Neurorehab Neural Re*. 2009;23:879–85. doi:10.1177/1545968309338193
- Pereira AC, Huddleston DE, Brickman AM, Sosunov A, Hen R, McKhann G, et al. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *P Natl Acad Sci USA*. 2007;104:5638–43. doi:10.1073/pnas.0611721104
- Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, et al. Effects of aerobic exercise on mild cognitive impairment. *Arch Neurol-Chicago*. 2010;67:71–9. doi:10.1001/archneurol.2009.307
- Bohannon RW. Comfortable and maximum walking speed of adults aged 20–79 years: reference values and determinants. *Age Ageing*. 1997;26:15–9. doi:10.1093/ageing/26.1.15
- Perry J, Garrett M, Gronley JK, Mulroy S. Classification of walking handicap in the stroke population. *Stroke*. 1995;26:982–9.
- Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Resp Crit Care*. 1998;158:1384–7.
- Eng JJ, Dawson AS, Chu KS. Submaximal exercise in persons with stroke: test–retest reliability and concurrent validity with maximal oxygen consumption. *Arch Phys Med Rehabil*. 2004;85:113–8. doi:10.1016/S0003-9993(03)00436-2
- Tang A, Sibley K, Bayley M, McIlroy W, Brooks D. Do functional walk tests reflect cardiorespiratory fitness in sub-acute stroke? *J Neuroeng Rehabil*. 2006;3:23–30. doi:10.1186/1743-0003-3-23
- Potempa K, Lopez M, Braun LT, Szidon P, Fogg L, Tincknell T. Physiological outcomes of aerobic exercise training in hemiparetic stroke patients. *Stroke*. 1995;26:101–5.
- Rimmer JH, Rauworth AE, Wang EC, Nicola TL, Hill B. A preliminary study to examine the effects of aerobic and therapeutic (nonaerobic) exercise on cardiorespiratory fitness and coronary risk reduction in stroke survivors. *Arch Phys Med Rehabil*. 2009;90:407–12. doi:10.1016/j.apmr.2008.07.032
- Rippe JM, Ward A, Porcari JP, Freedson PS. Walking for health and fitness. *J Am Med Assoc*. 1988;259:2720–4. doi:10.1001/jama.259.18.2720
- Ivey FM, Macko RF, Ryan A, HAfer-Macko CE, Goldberg AP. Treadmill aerobic training improves glucose tolerance and indices of insulin sensitivity in disabled stroke survivors: a preliminary report. *Stroke*. 2007;38:2752–8. doi:10.1161/STROKEAHA.107.490391
- Rimmer JH, Riley B, Creviston T, Nicola T. Exercise training in a predominantly African-American group of stroke survivors. *Med Sci Sport Exerc*. 2000;32:1990–6. doi:10.1097/00005768-200012000-00004
- Lennon O, Carey A, Gaffney N, Stephenson J. A pilot randomized controlled trial to evaluate the benefit of the cardiac rehabilitation paradigm for the non-acute ischaemic stroke population. *Clin Rehabil*. 2008;22:125–33. doi:10.1177/0269215507081580
- Duncan P, Studenski S, Richards L, Gollub S, Lai SM, Reker DM, et al. Randomized clinical trial of therapeutic exercise in subacute stroke. *Stroke*. 2003;34:2173–80. doi:10.1161/01.STR.0000083699.95351.F2

39. Tang A, Sibley KM, Thomas SG, Bayley M, Richardson D, McIlroy WE, et al. Effects of an aerobic exercise program on aerobic capacity, spatiotemporal gait parameters, and functional capacity in subacute stroke. *Neurorehab Neural Re*. 2009;23:398–406. doi:10.1177/1545968308326426
40. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *New Engl J Med*. 2002;346:793–801. doi:10.1016/S1062-1458(02)00697-9
41. Eich HJ, Werner C, Hesse S. Aerobic treadmill plus Bobath walking training improves walking in subacute stroke: a randomized controlled trial. *Clin Rehabil*. 2004;18:640–51. doi:10.1191/0269215504cr779oa
42. Pohl M, Werner C, Holzgrafe M, Kroczeck G, Mehrholz J, Wingendorf I. Repetitive locomotor training and physiotherapy improve walking and basic activities of daily living after stroke: a single-blind, randomized multicentre trial (DEutsche GAngtrainerStudie, DEGAS). *Clin Rehabil*. 2007;21:17–27. doi:10.1177/0269215506071281
43. Tilson J, Sullivan K, Cen S, Rose D, Koradia C, Azen S, et al. Meaningful gait speed improvement during the first 60 days poststroke: minimal clinically important difference. *Phys Ther*. 2010;90:196–208. doi:10.2522/ptj.20090079
44. Fulk GD, Echternach JL, Nof L, O'Sullivan S. Clinometric properties of the six-minute walk test in individuals undergoing rehabilitation poststroke. *Physiother Theory Pract*. 2008;24:195–204. doi:10.1080/09593980701588284
45. Cohen JJ, Sveen JD, Walker JM, Brummel-Smith K. Establishing criteria for community ambulation. *Top Geriatr Rehabil*. 1983;1:71–7.
46. Globas C, Macko RF, Luft AR. Role of walking-exercise therapy after stroke. *Expert Rev Cardiovasc Ther*. 2009;7:905–10. doi:10.1586/erc.09.58
47. Luft AR, Macko RF, Forrester LW, Villagra F, Ivey F, Sorkin JD, et al. Treadmill exercise activates subcortical neural networks and improves walking after stroke: a randomized controlled trial. *Stroke*. 2008;39:3341–50. doi:10.1161/STROKEAHA.108.527531
48. Katz-Leurer M, Shochina M, Carmeli E, Friedlander Y. The influence of early aerobic training on the functional capacity in patients with cerebrovascular accident at the subacute stage. *Arch Phys Med Rehabil*. 2003;84:1609–14. doi:10.1053/S0003-9993(03)00344-7
49. Huang HC, Chung KC, Lai DC, Sung SF. The impact of timing and dose of rehabilitation delivery on functional recovery of stroke patients. *J Chin Med Assoc*. 2009;72:257–64. doi:10.1016/S1726-4901(09)70066-8
50. Carmichael ST. Cellular and molecular mechanisms of neural repair after stroke: making waves. *Ann Neurol*. 2006;59:735–42. doi:10.1002/ana.20845
51. Chu KS, Eng JJ, Dawson AS, Harris JE, Ozkaplan A, Glyfadóttir S. Water-based exercise for cardiovascular fitness in people with chronic stroke: a randomized controlled trial. *Arch Phys Med Rehabil*. 2004;85:870–4. doi:10.1016/j.apmr.2003.11.001
52. Eng JJ, Chu KS, Kim CM, Dawson AS, Carswell A, Hepburn KE. A community-based group exercise program for persons with chronic stroke. *Med Sci Sport Exerc*. 2003;35:1271–8. doi:10.1249/01.MSS.0000079079.58477.0B
53. Pang MYC, Eng JJ, Dawson AS, McKay HA, Harris JE. A community-based fitness and mobility exercise program for older adults with chronic stroke: a randomized, controlled trial. *J Am Geriatr Soc*. 2005;53:1667–74. doi:10.1111/j.1532-5415.2005.53521.x
54. Tang A, Marzolini S, Oh P, McIlroy W, Brooks D. Feasibility and effects of adapted cardiac rehabilitation after stroke: a prospective trial. *BMC Neurol*. 2010;40. doi:10.1186/1471-2377-10-40
55. Macko RF, Smith GV, Dobrovolsky CL, Sorkin JD, Goldberg AP, Silver KH. Treadmill training improves fitness reserve in chronic stroke patients. *Arch Phys Med Rehabil*. 2001;82:879–84. doi:10.1053/apmr.2001.23853
56. Kodama S, Tanaka S, Saito K, Shu M, Sone Y, Onitake F, et al. Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: a meta-analysis. *Arch Intern Med*. 2007;167:999–1008. doi:10.1001/archinte.167.10.999
57. Brawner CA, Ehrman JK, Schairer JR, Cao JJ, Keteyian SJ. Predicting maximum heart rate among patients with coronary heart disease receiving beta-adrenergic blockade therapy. *Am Heart J*. 2004;148:910–4. doi:10.1016/j.ahj.2004.04.035
58. Pang MYC, Eng JJ. The use of aerobic exercise training in improving aerobic capacity in individuals with stroke: a meta-analysis. *Clin Rehabil*. 2006;20:97–111. doi:10.1191/0269215506cr926oa
59. Macko R, Ivey FM, Forrester LW, Hanley D, Sorkin JD, Katznel LI, et al. Treadmill exercise rehabilitation improves ambulatory function and cardiovascular fitness in patients with chronic stroke: a randomized, controlled trial. *Stroke*. 2005;36:2206–11. doi:10.1161/01.STR.0000181076.91805.89
60. Shaughnessy M, Resnick B, Macko R. Testing a model of poststroke exercise behavior. *Rehabil Nurs*. 2006;31:15–21.