Chronic Effects and Acute Physiological Response to Aerobic and Resistance Training in Patients Following Stroke Referred to a Cardiac Rehabilitation Program

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Institute of Medical Science
University of Toronto

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Abstract

There is compelling evidence that regular physical activity is likely to play a role in the secondary prevention of stroke and comorbid coronary artery disease. However, structured physical activity programs are not widely available for people following stroke. Cardiac rehabilitation programs (CRP) are well suited to provide exercise training following traditional stroke rehabilitation. However, people following stroke may be limited by a constellation of neurological deficits that may prevent them from effectively participating in and benefiting from an adapted CRP.
Accordingly, the objectives of this work were to 1) examine the utility of cardiopulmonary exercise stress testing (CPET) for developing an exercise prescription in people ≥3 months post-stroke with mild/moderate motor impairments 2) determine ability to achieve minimal recommended exercise training levels reported to elicit health benefits during a single standard CR session following completion of a CRP 3) evaluate the physiological, and cognitive effects of a 24-week CRP of resistance and aerobic exercise and the effect of stroke-recovery-time. It was hypothesized that most patients (>50%) would reach a level of exertion on the CPET that would provide recommended exercise prescription target levels and that individuals would be able to systematically reach these target levels during a CR session. Moreover, the established exercise program would result in physiological and cognitive benefit independent of time-from-stroke.

Study 1 demonstrated that most patients achieved a level of exertion during the CPET sufficient to inform an exercise prescription. In Study 2 patients with motor impairments were able to meet or exceed minimal recommended exercise target levels of intensity, duration and energy expenditure. In Study 3 a CRP yielded improvements over multiple domains of recovery (\( \text{VO}_{2\text{peak}} \), functional ambulation, sit-to-stand performance, and muscular strength). While those referred ≤1 year and >1 year post-stroke derived benefits from a CRP, those who started earlier (≤1 year) had greater improvements in ambulatory performance. In Study 4 combined aerobic and resistance exercise resulted in improvements in cognitive function. Change in cognition was positively associated with change in fat-free mass and change in anaerobic threshold. In summary people post-stroke are able to effectively participate in and benefit from an adapted CRP.
Acknowledgments

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# Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>1RM</td>
<td>One repetition maximum</td>
</tr>
<tr>
<td>6MWD</td>
<td>Six minute walk distance</td>
</tr>
<tr>
<td>ADL</td>
<td>Activities of daily living</td>
</tr>
<tr>
<td>AT</td>
<td>Aerobic training</td>
</tr>
<tr>
<td>BDNF</td>
<td>Brain-derived neurotrophic factor</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass graft surgery</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>CES-D</td>
<td>Centre for Epidemiological Studies Depression</td>
</tr>
<tr>
<td>CMSA</td>
<td>Chedoke-McMaster Stroke Assessment</td>
</tr>
<tr>
<td>CPET</td>
<td>Cardiopulmonary exercise test</td>
</tr>
<tr>
<td>CR(P)</td>
<td>Cardiac rehabilitation (program)</td>
</tr>
<tr>
<td>CRA</td>
<td>Clinically relevant abnormality</td>
</tr>
<tr>
<td>DXA</td>
<td>Dual energy x-ray absorptiometry</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EE</td>
<td>Energy expenditure</td>
</tr>
<tr>
<td>FFM</td>
<td>Fat-free mass</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health related quality of life</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Insulin like growth factor-I</td>
</tr>
<tr>
<td>LAD</td>
<td>Large artery disease</td>
</tr>
<tr>
<td>METS</td>
<td>Multiples of resting metabolic rate</td>
</tr>
<tr>
<td>MDC</td>
<td>Minimal detectable change</td>
</tr>
<tr>
<td>MCI</td>
<td>Mild cognitive impairment</td>
</tr>
<tr>
<td>MoCA</td>
<td>Montreal Cognitive Assessment</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous Coronary Intervention</td>
</tr>
<tr>
<td>RMR</td>
<td>Resting metabolic rate</td>
</tr>
<tr>
<td>ROM</td>
<td>Range of motion</td>
</tr>
<tr>
<td>RPE</td>
<td>Rating of perceived exertion</td>
</tr>
<tr>
<td>RT</td>
<td>Resistance training</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>SIS</td>
<td>Stroke Impact Scale</td>
</tr>
<tr>
<td>SAD</td>
<td>Small artery disease</td>
</tr>
<tr>
<td>TRI-REPS</td>
<td>Toronto Rehabilitation Institution’s Risk Factor Modification and Exercise Program following Stroke</td>
</tr>
<tr>
<td>TSR</td>
<td>Traditional stroke rehabilitation</td>
</tr>
<tr>
<td>VO$_{2\text{peak}}$</td>
<td>Peak oxygen uptake</td>
</tr>
<tr>
<td>VO$_{2\text{max}}$</td>
<td>Maximal oxygen uptake</td>
</tr>
<tr>
<td>VAT</td>
<td>Ventilatory anaerobic threshold</td>
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<tr>
<td>VPB</td>
<td>Ventricular premature beat</td>
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Chapter 1 INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

Stroke is the leading cause of long-term neurological disability in North America (Centre for Chronic Disease Prevention and Control, 2001, Gordon et al., 2004). It is estimated that 300,000 Canadians are presently living with the effects of a stroke. Of the 40,000 to 50,000 people who are diagnosed with stroke annually in Canada, approximately a third of these are recurrent cases of stroke (Heart and Stroke Foundation of Canada, 2007). Post stroke survival is significantly affected by concomitant coronary artery disease (CAD), the incidence of which has been reported to occur in up to 75% of stroke survivors (Roth 1993). This is not surprising considering that both stroke and CAD share links with many of the same modifiable risk factors. Physical inactivity is a particularly powerful risk factor for both stroke and CAD and has been identified by the INTERSTROKE study as one of the 5 main health hazards accounting for more than 80% of the global risk of stroke (O'Donnell et al. 2010). A review conducted by Katzmarzyk et al. reported that lack of physical activity carried a relative risk of 1.60 for stroke, similar to or higher than that for CAD and other diseases (Katzmarzyk and Janssen 2004). Moreover, a recent cross sectional study of US civilians with previous stroke (n=388) demonstrated that regular exercise and abstinence from smoking were independently associated with lower all-cause mortality after stroke (Towfighi, Markovic and Ovbiagele 2012).

Despite the importance of physical activity for people following stroke, few stroke survivors exercise regularly (Michael and Macko 2007; Rand et al. 2009; Towfighi, Markovic and Ovbiagele 2012). This may be because structured programs that are aimed at reducing risk of recurrent stroke and comorbid cardiac disease are not widely available or accessible (Fullerton et al. 2008; Rimmer et al. 2005). This is of concern as many of the modifiable risk factors are increasing in prevalence in the Canadian population, specifically physical inactivity, diabetes, and obesity, which when combined with the growing elderly population will likely result in an increased number of individuals living with the effects of stroke (Gillum and Sempos 1997).
1.1.2 Cardiac Rehabilitation Following Stroke and Gaps in the Literature

Evidence is accumulating that cardiac rehabilitation (CR) programs can provide exercise programming for individuals following traditional stroke rehabilitation (TSR) (Tang et al. 2010; Lennon et al. 2008). Given the elevated risk for recurrent stroke and potential for exercise to mediate many of the modifiable stroke risk factors (Gordon et al. 2004), the exercise training components as well as risk factor assessment, education and interventions offered by interprofessional health care CR teams are suited to long-term health behavior change appropriate for individuals following stroke. These include aerobic and resistance training, nutrition and psychosocial counseling as well as cardiopulmonary exercise stress testing (CPET). In view of the high incidence of coexisting health issues such as diabetes and coronary artery disease, these components are important but may not be available in a TSR facility.

Despite exercise being an important component of rehabilitation programs, there are a number of issues surrounding the feasibility and efficacy of CR programming for people following stroke that remain unresolved or require further investigation. One such issue relates to the process of exercise prescription. There is a dearth of information on the clinical utility and feasibility of the CPET for prescribing exercise to individuals with a history of stroke prior to engaging in exercise. Measures derived from the CPET guide appropriate exercise prescriptions that determine safe and efficacious exercise. The most important parameter of the prescription is that of intensity (Rimmer et al. 2009; Kavanagh et al. 2002; Gormley et al. 2008), and it is believed to be the primary factor responsible for change in peak oxygen uptake (VO\textsubscript{2peak}) (Lam et al. 2010; Gormley et al. 2008). A higher VO\textsubscript{2peak} is associated with lower stroke risk in males (Kurl et al. 2003; Lee and Blair 2002), as well as lower mortality in cardiac patients (Kavanagh et al. 2002). Moreover, evidence that the intensity of physical activity (moderate to high) may be a greater determinant of stroke prevention than duration of exercise is accumulating (Willey et al. 2009; Lee, Folsom and Blair 2003). In view of the importance of exercise intensity, an exercise prescription based on objective measures derived from a CPET is important. Yet no study has examined the utility of the CPET for prescribing exercise to people following stroke.
While determining target exercise levels recommended to elicit health benefits through CPET assessment is important for developing safe and efficacious exercise programs, the ability of stroke patients to achieve these recommended target exercise levels during a typical CR session have not been investigated. Of concern is that physical activity levels may be limited by a constellation of neurological impairments as well as comorbidities. Yet, no study has examined if patients following stroke participating in a CR program can achieve the recommended minimal exercise training intensity, duration, and energy expenditure levels reported to elicit health benefits.

Establishing the feasibility of CPETs for determining target exercise levels, and determining the ability of people following stroke to achieve these target levels during a CR session would be of limited importance if the exercise program did not result in favorable outcomes to the individual. While evidence is accumulating that participation in adapted CR programs result in gains in cardiovascular fitness post-stroke (Tang et al. 2010; Lennon et al. 2008), other parameters of stroke recovery such as muscle weakness, ambulatory limitations, sit-to-stand performance, and cognitive impairment are also important. Yet, no study has examined if an adapted CR program will elicit improvements beyond the reported gain in $\dot{V}O_{2\text{peak}}$. Nor has any study examined the efficacy of adapted CR treatments in relation to time elapsed post-stroke. This issue merits attention as participants of adapted CR programs are typically referred at least 3 months to more than 5 years following the index stroke event (Tang et al. 2010; Lennon et al. 2008).

Determining if there are greater benefits to be derived from referring patients earlier or later after stroke, and if a CR intervention results in ancillary benefits in addition to improvements in $\dot{V}O_{2\text{peak}}$, will have important clinical implications for best practice guidelines.

Knowledge of the long-term effects and acute physiological response to exercise in patients following stroke will provide valuable information that will addresses specific gaps in the literature as well as provide clinicians with the knowledge to effectively conduct an adapted CR program for people following stroke. Therefore, the objectives of this work were 1) to examine the utility of the CPET for developing an exercise prescription for people $\geq$3 months following stroke with motor impairments 2) determine if people following stroke can achieve minimal
recommended exercise training levels reported to elicit health benefits during a single standard CR sessions following completion of a CR program, 3) to evaluate the physiological and cognitive effects of a 24-week CR program of resistance and aerobic exercise and effect of stroke-recovery-time in consecutively enrolled patients with motor impairments.

1.2 Acute and Chronic Physiological Response to Exercise and Implications for Exercise Prescription

This section of the review will provide the rationale and background for the studies presented in Chapters 2 and 3 examining the acute physiological response to exercise. For both of these studies it is important to examine the evidence surrounding the dose-response relationship between exercise and health related outcomes in order to determine effective target exercise training levels. One of the challenges facing the exercise specialist is to prescribe the quantity and quality of exercise that will result in improvements in cardiovascular fitness and modification of other risk factors without precipitating vascular complications. In this review, the intensity parameter of the exercise prescription emerges as the most important parameter of the exercise prescription for the exercise specialist to consider, both from a safety and efficacy point-of-view. Yet, the current exercise recommendations (ACSM 2009; Gordon et al. 2004) have been established based on studies that have included only able bodied people. While these guidelines may be applied to other populations (Garber et al. 2011), individuals with neurological deficits may not be able to reach these minimal target levels during a typical exercise session which would render the targets ineffectual. Also, target exercise levels, specifically related to the parameter of intensity, are largely quantified relative to an individuals’ maximal functional capacity assessed by a CPET. Establishing the utility of the CPET for determining these target levels is the first step in establishing the feasibility of a systematic exercise prescription process. Therefore, the available evidence for the feasibility and utility of the CPET for determining these targets will also be presented herein. Section 1.3 will provide a review of the chronic effects of aerobic and resistance exercise in people following stroke and provide the rationale and background for the studies presented in Chapters 4 and 5.
1.2.1 Dose Response Relationship between Exercise and Health Related Outcomes in Healthy Adults and those with Cardiovascular Disease

There is a growing body of research that has been completed in the effort to determine minimal and safe upper limits of physical activity to improve cardiovascular fitness and other health related outcomes in healthy adults and those recovering from CAD. Overall, the evidence supports a linear dose-response relationship such that the greater the dose of exercise, the more benefit accrued (Garber et al. 2011; Kesaniemi, Danforth and Jensen 2001; Bouchard 2001) with mortality benefit occurring with as little as 15 minutes of exercise on most days of the week in sedentary individuals (Wen et al. 2011). However, evidence is emerging that there may be a safe upper limit of exercise beyond which musculoskeletal issues, abnormal heart rhythms, scarring of the myocardium, and cardiac remodeling may occur (Ector et al. 2007; La Gerche et al. 2012; Maron and Pelliccia 2006; Mont, Elosua and Brugada 2009). However, these adverse events are reported to occur in people training and competing in extreme exercise events such as ultramarathons, marathons, and ironman distance triathalons; a dose of exercise beyond that which would be prescribed for people with cardiovascular disease and thus will not be discussed herein.

The activity parameters of the exercise prescription (frequency, intensity, duration, type of exercise) determine the “dose” of exercise and are important determinants of cardiovascular fitness, improved body composition, and modification of other risk factors (reduced hypertension, improved blood lipid profile, enhanced glucose regulation). The intensity and duration of exercise determine the caloric expenditure of the exercise session; however, not all benefits of physical activity occur at the same exercise intensity. For example, in healthy adults and those with cardiovascular disease, low intensity, long duration exercise may result in weight loss (Church et al. 2007; Ades et al. 2009) but greater improvements in $\text{VO}_{2\text{peak}}$ require higher intensity exercise (Gormley et al. 2008; Gossard et al. 1986; Kraus et al. 2002; O’Donovan et al. 2005). The effect of these exercise parameters on modulation of cardiovascular risk factors may play a role in reducing morbidity and mortality in people following stroke (Gordon et al. 2004).
Yet, there is a dearth of adequately powered studies evaluating the dose-response relationship between exercise and cardiovascular disease risk factors in people following stroke. A study conducted by Rimmer and colleagues examined the effects of different exercise interventions in people following stroke (Rimmer et al. 2009). Fifty-five individuals with unilateral ischemic stroke were assigned to one of three groups; either 30 minutes of moderate intensity exercise (69% of heart rate reserve determined by graded exercise stress test), 60 minutes of low intensity exercise (50% of heart rate reserve), or to a therapeutic exercise group. After 14 weeks of exercise training, the group participating in 30 minutes of moderate intensity exercise had significantly greater improvements in systolic and diastolic blood pressure, and blood lipid levels than the group participating in 60 minute of low intensity exercise or therapeutic exercise. No other studies have provided data elucidating the dose-response relationship between exercise and risk factor modification in people following stroke.

The results from Rimmer et al. support the evidence from retrospective and prospective studies demonstrating the importance of exercise intensity (Blair et al. 1995; Kavanagh et al. 2002; Willey et al. 2009; Lee, Folsom and Blair 2003; Lee and Paffenbarger 1998; Willey et al. 2011). These studies suggest that intensity of physical activity and cardiovascular fitness level are positively associated with lower primary stroke risk, as well as lower mortality rates in individuals with CAD and in healthy adults. Collective findings from the Northern Manhattan Studies (Willey et al. 2009; Willey et al. 2011) reveal that the intensity of physical activity may be a greater determinant of primary ischemic stroke prevention (including silent brain infarcts) than total energy expenditure or duration of exercise. In the first of two prospective cohort studies, physical activity behavior was measured by in-person questionnaire in 3,298 people living in Northern Manhattan. The questionnaire measured the duration and frequency of leisure-time and recreational activity. Intensity of the activity and energy expenditure in kilocalories was calculated based on the compendia of physical activities. Light activity was defined as an activity requiring an intensity level between 1 and 5.5 times resting metabolic rate (MET), moderate was 5.5 to 8 METs and heavy was >8 METs. The findings demonstrated that moderate to high intensities of physical activity (usual activities of daily living excluded) were associated with a lower risk of primary ischemic stroke even after accounting for other stroke risk factors. Light activity or total energy expenditure was not associated with the same benefit.
and the protective effect was only observed in men. The non significant dose response association between exercise intensity and lower risk of primary ischemic stroke in women may have been owing to a misclassification of exercise in women. For example, an intensity of 5.5 METS, while classified as “light” activity for men, may be moderate to high intensity for women. The metric of exercise intensity (METs) is not relative to the individual’s functional capacity. A subsequent study conducted by the same group of investigators, was similar in design, but a magnetic resonance imaging assessment was conducted in a subsample of the population (n=1 290) (Willey et al. 2011). This study showed that engaging in moderate to heavy physical activity was associated with reduced subclinical brain infarcts with no effect from light intensity activity. Findings from other studies broadly support the association between exercise intensity and stroke risk. The Harvard Alumni Study demonstrated that light activity does not provide a protective effect for first ever stroke (Lee and Paffenbarger 1998) and a meta-analysis of cohort and case control studies conducted by Lee and colleagues support the evidence that higher intensity activity provides protection from stroke while lighter activity does not (Lee, Folsom and Blair 2003).

While questionnaire based studies that estimate physical activity tend to have a large measurement error and lack precision, other studies have demonstrated a relationship between mortality from cardiovascular disease and objective measures of physical activity (i.e. cardiovascular fitness; \( \text{VO}_{2\text{peak}} \)) (Lee and Blair 2002; Kavanagh et al. 2002; Kavanagh et al. 2003; Blair et al. 1995). In one of the earliest studies, Blair et al. measured maximal cardiovascular fitness by treadmill test in 9 777 healthy men ranging in age from 20 to 82 years of age, at two time points conducted a mean of 4.9 years apart. Among those who demonstrated an increase in physical fitness, there was a 44% reduction in mortality risk (95% CI; 25-29%) relative to men who remained unfit. Moreover, people who improved fitness were less likely to die from cardiovascular disease (Blair et al. 1995).

In view of the above, it is important to determine strategies to optimize cardiovascular fitness. There is a well established evidence base that suggests that the intensity of physical activity is the primary factor responsible for change in \( \text{VO}_{2\text{peak}} \) (Gormley et al. 2008; Lam et al. 2010; Swain 2005; Swain and Franklin 2002). In a well designed study, Gormley et al. randomly assigned 61
healthy subjects matched for sex and \( \dot{V}O_{2\text{max}} \) to moderate, vigorous, near-maximal-intensity, or a non exercising control group (Gormley et al. 2008). Subjects were required to maintain predetermined exercise heart rates based on a heart rate reserve formula. The moderate exercise group was prescribed an intensity equivalent to 50% of \( VO_2 \) reserve, vigorous was 75% of \( VO_2 \) reserve, and near maximal intensity was 95% \( VO_2 \) reserve. In order to equalize exercise volume and energy expenditure across groups, duration and frequency of exercise were varied appropriately. There was a significant improvement in \( \dot{V}O_{2\text{max}} \) (\( \text{ml} \cdot \text{kg} \cdot \text{min}^{-1} \)) in all exercising groups at a magnitude of 20.6% in the near-maximal, 14.3% in the vigorous, and 10% in the moderate-intensity group. There was a non-significant increase of 1.9% in the non exercising control group. All changes were significantly different from each other. Several other randomized studies support the importance of exercise intensity for optimizing cardiovascular fitness and reducing cardiovascular risk (Gossard et al. 1986; Kraus et al. 2002; O’Donovan et al. 2005). In total, these data support the importance of the intensity parameter of the exercise prescription. While there is evidence supporting a link between peak oxygen uptake as a mediator of lower mortality in cardiac patients (Kavanagh et al. 2002), any benefit to people following stroke requires validation from appropriately designed studies.

### 1.2.2 Exercise Prescription and Cardiopulmonary Exercise Stress Testing in Patients with Chronic Stroke

In view of the importance of exercise intensity, exercise prescriptions based on objective measures derived from a CPET are important. A CPET involves measuring oxygen uptake, carbon dioxide output and minute ventilation, while monitoring blood pressure, and 12-lead electrocardiogram (ECG). The CPET objectively evaluates cardiorespiratory fitness or \( \dot{V}O_2\text{peak} \), which is inversely related to both death from all causes as well as specific to cardiovascular disease (Myers et al. 2002). In addition, the CPET reveals myocardial ischemia, electrical instability, and exercise related symptoms.

For the clinician concerned about prescribing safe therapeutic exercise to people following stroke, information regarding risk and prevention of precipitating vascular complications is of paramount importance. While early post stroke the most common vascular event is another
stroke (Vickrey et al. 2002), five years post stroke there are twice as many deaths from myocardial infarction as there are from recurrent stroke (Hankey et al. 2000; Dhamoon et al. 2006). Most of the studies examining prevalence of signs and symptoms of CAD in those with stroke and transient ischemic attack have enrolled patients early after the event (Rokey et al. 1984; Amarenco et al. 2011; Di Pasquale et al. 1986). In the most recent study, Amarenco et al. reported that coronary plaques on angiography were present in 61.9% of 405 patients measured a median of 8 days after cerebral infarction (Amarenco et al. 2011). Coronary stenoses of ≥50% were found in 25.7% of these patients and 20 to 40% demonstrated silent ischemia. The marked prevalence of silent ischemia is of clinical importance as it is a condition that would go largely undiagnosed without a CPET or other investigation as individuals would not experience symptoms during exercise at or above the ischemic threshold. While, evidence of underlying CAD is common early post-stroke, it is likely that the incidence of abnormalities escalate as time from index stroke event increases. Sedentary behavior following stroke and the presence of risk factors common to stroke and CAD may be contributing factors. Also, many of the risk factors associated with CAD and stroke (hypertension, diabetes and obesity) are untreated in community-dwelling stroke survivors (Kopunek et al. 2007), further augmenting the risk associated with exertion. Thus it has been recommended that exercise prescriptions be based on the results of an exercise stress test with ECG monitoring for people following stroke (Gordon et al. 2004). This suggests that conducting CPETs prior to participation in a structured exercise program would be of particular importance in a CR setting as patients begin participation up to a mean of 5 years post-stroke (Lennon et al. 2008; Tang et al. 2010).

Unfortunately, best practice recommendations to guide intensity and duration of exercise treatments following stroke are mostly based on guidelines derived from other populations (ACSM 2009; Gordon et al. 2004). Nevertheless, these guidelines can be applied to conditions such as stroke, as long as exercise prescriptions are individualized according to parameters such as those determined by CPET (cardiovascular fitness level, hemodynamic response to exercise, signs or symptoms of CAD) as well as disability dimension, comorbid conditions, and health status (Garber et al. 2011). The American Heart Association guidelines for individuals with stroke recommend that to achieve a cardiovascular training effect, 20 to 60 minutes of continuous or accumulated exercise, 3
to 7 days per week at an intensity of 40 to 70% of $\dot{V}O_{2\text{peak}}$ or heart rate reserve should be performed (Gordon et al. 2004). However, a measure of exercise intensity that is relative to achievement of a percentage of $\dot{V}O_{2\text{peak}}$ versus $\dot{V}O_{2\text{max}}$ may vary depending on CPET performance as stroke-related factors unrelated to cardiovascular endpoints (e.g., neuromuscular disability, cognitive deficits) may affect termination of the test. Therefore, another important target intensity level for the prescription of exercise is the ventilatory anaerobic threshold (VAT) (Gordon and Scott 1995; Dwyer 1994; Tabet et al. 2006). The VAT is a submaximal intensity measure that does not necessitate the achievement of a “true” $\dot{V}O_{2\text{max}}$ on the CPET in order to be determined (i.e. an individual’s maximal capacity to transport and use oxygen). It represents the movement from aerobic to anaerobic metabolism and is recommended as an appropriate target intensity level for the prescription of exercise in healthy individuals and those with cardiovascular disease (Gordon and Scott 1995; Dwyer 1994; Tabet et al. 2006; Wasserman et al. 1973). Moreover, exercising at levels above the VAT have been shown to result in an over proportional rise in plasma catecholamines (Urhausen et al. 1994) and in cardiac patients a reduction in left ventricular ejection fraction (Koike et al. 1989) which could have pro arrhythmic consequences (Kohl et al. 1992).

Therefore, $\dot{V}O_{2\text{max}}$, VAT and the level at which a clinically relevant abnormality occurs are all critical measures for prescribing an exercise intensity that is both safe and effective. However, people who have had a stroke may be limited by a constellation of motor and neurological impairments that may prevent them from reaching these critical levels. These limitations may discourage the systematic application of CPETs for individuals following stroke. Unfortunately, few data are available to substantiate the feasibility and safety of graded exercise tests with ECG monitoring following chronic stroke. Lacking this information has hindered the development of exercise programs tailored to the functional capacities of survivors of stroke.

**Test-Retest Reliability of Cardiopulmonary Exercise Tests in Chronic Stroke**

Results of studies that have examined the reliability of CPETs in chronic stroke reveal a high level of test-retest reliability. In a study conducted by Potempa et al., 25 individuals with
chronic stroke exhibiting hemiparesis were tested twice on a cycle ergometer 48 hours apart (Potempa et al. 1995). The intraclass correlation coefficient and coefficients of determination for \( \dot{VO}_{2\text{max}} \), were both 0.94 indicating a high level of reliability. Further, Dubrovolny et al. examined the test-retest reliability of CPETs measured during peak and submaximal treadmill walking (fixed intensity) in 53 subjects >6 months post-stroke with gait-impairments (Dobrovolny et al. 2003). Data analysis revealed high reliability results for \( \dot{VO}_{2\text{peak}} \) (r=0.92), and submaximal \( VO_2 \) (r=0.89). Finally, Eng et al. measured test-retest reliability of \( \dot{VO}_{2\text{peak}} \) on the upright cycle in 12 community dwelling individuals a mean of 3 years post stroke with moderate stroke deficits (Eng, Dawson and Chu 2004). Reliability was excellent with an intraclass correlation coefficient of 0.93. While not the primary aim of the study, all 12 patients were reported to have reached a true \( \dot{VO}_{2\text{max}} \) (an individual’s maximal capacity to transport and use oxygen). However the definition of this criterion variable was very broad, including patients who reached a subjective measure of “volitional fatigue” normally deemed a \( \dot{VO}_{2\text{peak}} \) which limits the interpretation of this data. While results of these studies provide compelling evidence of high test-retest reliability for measuring peak oxygen uptake, these data do not reflect the utility of the CPET for prescribing exercise to people following stroke and highlight the need for further studies to be conducted in this area.

1.2.3 Cardiovascular Response to Traditional Post-stroke Rehabilitation Therapy

Despite the growing evidence of the importance of improving cardiovascular fitness through regular physical activity, the current traditional stroke rehabilitation (TSR) model is not designed with the goal of achieving these exercise targets within the therapy session. Rather, such programs are focused on functional retraining (mobility and self-care tasks), are delivered in the early recovery period, and are of short duration (usually 12 weeks). Moreover, CPET assessments are not available to most TSR programs and thus exercise cannot be tailored to the functional capacity of the individual following stroke.
Two studies have examined the cardiovascular response to exercise in the stroke population. MacKay-Lyons and Makrides evaluated the heart rate response of stroke survivors in physical and occupational therapy sessions (TSR) and revealed that participants reached at least the minimal target heart rate zone (40% of heart rate reserve) for less than 3 minutes of each session (mean of 54.8±7.2 minutes for physical and 40.8±7.0 minutes of occupational therapy), suggesting an insufficient training stimulus (MacKay-Lyons and Makrides 2002). This study demonstrated quantitatively the inadequacy of TSR for eliciting a cardiovascular stimulus. Following this, Kuys et al. monitored heart rate and recorded video during physiotherapy session in 30 individuals a mean of 30 weeks post-stroke (Kuys, Barauer and Ada 2006). Patients reached a mean exercise intensity of 24% of estimated heart rate reserve during the sessions (mean duration of sessions was 52±9.5 minutes) and 21 minutes participating in standing and walking activities. In concordance with the study of MacKay-Lyons et al., the exercise intensity was not sufficient to elicit a cardiovascular benefit. However, a limitation of these studies was the use of only heart rate to monitor exercise intensity. Heart rate is a poor reflection of exercise intensity in this population as approximately a third of stroke survivors are prescribed medications such as beta-blockers (Tang et al. 2010) that have varying effects on the heart rate response to exercise throughout the day, rendering the relation between heart rate and exercise intensity difficult to interpret even when using a beta-blocker adjusted target heart rate.

Moreover, the heart rate/VO₂peak relationship will vary when exercising in hot humid conditions, between different modes of exercise, in an altered hydrated state, and during sustained static exercise (reduced venous return and activation of baroreceptor reflex) (Smith and Mitchell 1995). Also, while daily exercise intensity and duration targets are of importance, accumulated exercise measured by weekly energy expenditure should also be considered. Based on the dose-response relationship between exercise and health related outcomes, the recommended energy expenditure (product of intensity and duration) from exercise that elicit benefits in health for most adults (i.e. lower rates of cardiovascular diseases and premature mortality) is approximately 1,000 kcal-wk⁻¹ (ACSM 2009; Garber et al. 2011). This translates to approximately 200 kcal/exercise session, 5 times-wk⁻¹. Unfortunately, energy expenditure was not measured in these studies and cannot be accurately calculated from duration of exercise and heart rate data.
Advances in technology make it possible to measure direct oxygen uptake during an exercise session with the use of a portable oxygen analyzer. This technology allows for accurate measures of total exercise energy expenditure (kilocalorie) and exercise intensity during an exercise session while not interfering with performance of the exercise. To our knowledge no study has directly examined the ability of stroke survivors in a long-term exercise program to systematically sustain exercise at an intensity and duration recommended for eliciting improvements in $\dot{V}O_2^{\text{peak}}$ and other health benefits.

1.3 Chronic Effects of Aerobic and Resistance Training Following Stroke

Despite improved acute medical management and advancement of pharmacological treatments for people with stroke, only approximately 14% of the individuals who survive a stroke will achieve complete recovery (Canning, Ada and O'Dwyer 2000; Flansbjer, Downham and Lexell 2006; Gordon et al. 2004; Michael and Macko 2007; Pound, Gompertz and Ebrahim 1998; Yaping et al. 2006). A profile of muscle weakness, ambulatory restrictions, cognitive impairment, and poor functional capacity is a common presentation post-stroke. Combined, these limitations likely contribute to the inadequate levels of physical activity common in people post-stroke (Michael and Macko 2007; Rand et al. 2009; Towfighi, Markovic and Ovbiagele 2012). Addressing these and other impairments through a supervised program of physical activity is likely to reduce the burden of these deficits and improve health related quality-of-life. In recognition of the importance of exercise programming as a clinical stream in post-stroke care, a number of health associations across North America have issued recommendations. The American Heart Association released a Scientific Statement in 2004 urging health care professionals to provide guidance on physical activity and exercise training for people following stroke (Gordon et al. 2004). There is also support here in Ontario for CR programs to provide exercise and secondary prevention programming following TSR. The Report of the Joint Stroke Strategy Working Group (Ontario Ministry of Health & Long Term Care) (2000) recommends that stroke prevention and cardiac rehabilitation and secondary prevention services link and share resources where feasible. Indeed, recent guidelines from the American Heart Association/American Stroke Association for the prevention of stroke in patients with stroke or transient ischemic attack recommends that guidance from a CR professional be considered upon initiation of an exercise regimen (Furie et al. 2011).
1.3.1 Cardiovascular Fitness

While there is support for the integration of CR programs in the care of people following stroke, only two studies have evaluated the efficacy of these programs and both were focused on one key exercise-related outcome, that being cardiovascular fitness (Tang et al. 2010; Lennon et al. 2008). In a single-blinded randomized control pilot study, Lennon and colleagues examined the cardiovascular effects of a CR program in 48 patients a mean of 5 years post-stroke (Lennon et al. 2008). Patients were randomized to either an exercise or non-exercising control group described as “usual care”. The exercise program included low-moderate intensity cycle ergometer exercise (50 to 60% of heart rate reserve), two times per week for 10 weeks. CR resulted in significantly greater improvements compared to controls in predicted \( \dot{V}O_2\text{peak} \) (mean change of 13.2 % vs. no mean change respectively). Unfortunately, the submaximal exercise testing protocol utilized in this study introduced a significant limitation to the results. Each patient cycled for 3 minutes at a fixed intensity of 5.6 Nm at 50 revolutions per minute without gas exchange measures after fasting for 12 hours. It was unclear why patients were tested at a fixed intensity or in a fasting state. Exercise after fasting is not recommended especially in those who may have coexisting diabetes. Moreover, a subsequent study conducted by the same authors demonstrated that equations to predict \( \dot{V}O_2\text{max} \) from submaximal effort using heart rate were not feasible for the majority of patients following stroke (Lennon et al. 2012). The authors cited age and use of beta-blockade medication as the two greatest barriers to the efficacy of submaximal test protocols.

Finally, in a study conducted in a CR facility, Tang et al. incorporated a repeated measures design with a 3 month non intervention baseline period followed by 6 months of adapted CR (Tang et al. 2010). The subjects were at least 3 months post-stroke with a moderate level of disability. The intervention included aerobic and resistance exercise one time per week at the CR centre. Patients were required to complete 4 additional aerobic and 1 to 2 additional resistance training sessions at home and this was tracked via exercise diary. Among the 38 patients completing the intervention, \( \dot{V}O_2\text{peak} \) improved significantly relative to the stable
baseline period (10%, p=0.046) and the change in VAT (8.1%) approached significance (p=0.06).

Numerous other studies conducted in a research setting, have shown that one component of CR, mainly regular aerobic exercise will evoke improvements in the cardiovascular fitness of stroke survivors. In a meta analysis conducted by Brazzelli et al., aerobic exercise (4 studies) and combined aerobic and resistance training (1 study) significantly improved \( \dot{V}O_{2\text{peak}} \) compared to controls (Brazzelli et al. 2011). Relative gains in \( \dot{V}O_{2\text{peak}} \) (mL·kg\(^{-1}\)·min\(^{-1}\)) in patients \( \geq 3 \) months post-stroke randomized to exercise training were in the range of 10.7% to 13.3% in 2 studies (Pang et al. 2005; Potempa et al. 1995) and as high as 17% reported in 1 study (Macko et al. 2005). These changes were significantly greater than changes demonstrated by the respective control groups. The relative magnitude of change in these studies is similar to that reported by Tang et al. in individuals participating in CR following stroke (mean change of 10%) and similar to that reported in cardiac patients (9-18%) participating in CR (Marzolini et al. 2008; Marzolini, Candelaria and Oh 2010; Milani, Lavie and Mehra 2004; Lavie and Milani 200). In addition, relative gains experienced by cardiac patients in VAT following an exercise program (2-11%) (Milani, Lavie and Mehra 2004; Marzolini et al. 2008; Carlson et al. 2000; Lavie and Milani 200) were similar to the 8.1% change reported by Tang et al. in patients participating in CR following stroke.

The documented gain in exercise capacity as a result of an exercise program may also have implications for activity of daily living (ADL) function in patients following stroke. For example, the mean peak oxygen uptake in stroke survivors is reported to be approximately 14 m\(\text{l}\)·kg\(\cdot\)min\(^{-1}\) (Ivey et al. 2005; Michael and Macko 2007; Smith, Saunders and Mead 2012). Generally, the oxygen requirements for carrying out activities of daily living fall within the range of 10 to 18 m\(\text{l}\)·kg\(\cdot\)min\(^{-1}\) (activities such as dressing, walking 4.3 kilometers per hour, making a bed) (Ivey et al. 2005). Thus, activities that may have been completed with ease prior to a stroke may become prohibitive post stroke due to the maximal strain that may be imposed on the cardiovascular system. Improvements as a result of regular physical activity in the magnitude described in published studies would likely elevate the threshold of tolerance for completion of
some ADLs. However, no studies have examined the effect of CR on ADL function in people following stroke.

### 1.3.2 Muscular Function

While studies examining the efficacy of CR programs have focused on cardiovascular fitness as the key outcome measure, benefit derived from the combined aerobic training (AT) and resistance training (RT) interventions offered in a CR program may extend to other dimensions of stroke recovery such as muscular strength, functional ambulation, and sit-to-stand performance but these have not yet been examined.

Weakness and fatigue are two common complaints from patients with stroke (Colle et al. 2006; Patten, Lexell and Brown 2004). Research has shown that strength is significantly diminished in both the affected and non-affected limbs of stroke survivors when compared to age matched able bodied subjects (Harris et al. 2001; Jorgensen and Jacobsen 2001). The ability to perform ADLs depends in part upon muscular function. When muscle function is attenuated post-stroke, activity can be limited (Canning, Ada and O'Dwyer 2000; Ottenbacher 1980). To stand up out of a chair, strength is needed in the lower limbs and trunk. Also, strength is correlated with walking speed, independence and distance as well as stair climbing and sit and stand performance (Morris, Dodd and Meg 2004). Therefore, determining strategies to improve muscular strength may translate to enhanced ADL function.

Although no study has examined the efficacy of CR in improving muscular strength, a recent meta analysis conducted by Brazzelli et al. examined outcomes from 10 studies (3 in sub acute stroke) assessing the effects of RT or combined AT+RT on muscle function (Brazzelli et al. 2011). The results were summarized as being inconsistent. These equivocal results may be related to many factors. The authors of the review postulated that it may be owing in part to methodological bias or an unequal training time. Careful inspection of the 7 studies conducted in patients in the chronic stage of stroke reveal several limitations in the study design and resistance training interventions (described below). Furthermore the benefit of pooled analyses was mitigated in this review of studies, with a bias towards results from a single study. Unfortunately, the one study (Donaldson et al.) included in 3 separate analyses as part of the
meta analysis exposed a small sample of patients (n=10) to only 6 weeks of an unconventional RT program (Donaldson et al. 2009).

In general, duration of the RT interventions included in the meta analysis were relatively short, with two studies exposing patients to only 6 weeks of RT (Kamimura and Ikuta 2002; Donaldson et al. 2009), both including only 10 participants per group and resulting in inconsistent findings. Time exposure to RT may be an important determinant of physiological change for people following stroke who are typically older and with more disability and coexisting chronic disease than in the general population (Pederson, Sen and Gordon 2011). Furthermore, most RT interventions included in the meta-analysis were either poorly described, of insufficient volume, or did not include progression of either weight load or repetitions required to elicit ongoing improvement. For example, Flansbjer et al. included only 6 minutes of RT two times per week for 10 weeks and Mead et al. included an intervention of only 4 RT exercises (Flansbjer et al. 2008). One study included a single measure of grip strength, however the RT exercises described were not targeting grip strength. They included arm exercises (push-ups in chair, weight lifting, water bottles, pulley) and back extension exercises (pulley, pull-down, walking stick, prone—extension) with other exercises targeting trunk and lower body (Langhammer, Lindmark and Stanghelle 2007). While some studies show that grip strength is related to global upper extremity activity (Boissy et al. 1999) others have found no association between change in grip strength and change in upper extremity strength over time (Renner, Bungert-Kahl and Hummelsheim 2009). Also, RT exercises that were included in a study conducted by Donaldson et al., the sole study included in three separate analyses, consisted of placing different food items in shopping bags, taking a pen cap on and off, reaching a shelf when seated, and moving items such as a bag of dried pasta or tin of baked beans. In this study, there was mention of a weight load being used to provide resistance, however it was unclear what type of weight was used.

RT may have varying effects on remediation of muscle weakness depending on the amount of time elapsed since time from stroke to the start of the intervention. Early post-stroke one of the underlying mechanisms for muscle weakness is loss of descending input to the spinal motor neurons, resulting in reduced activation of motor units (Hara et al. 2000). In the later chronic
stage of stroke, strength may be further attenuated by muscle mass loss owing to reduction in the number of motor units due to prolonged inactivity (Hara et al. 2000; Ryan et al. 2002). Therefore, separate sub analyses of the studies conducted in the sub acute and chronic stage of stroke would be beneficial for a better understanding of adaptation to RT interventions in people following stroke but was not included in the meta analysis conducted by Brazzelli et al. (Brazzelli et al. 2011)

*Measuring Muscle Performance*

The ability to perform ADLs depends in part upon muscular strength, endurance and power (Canning, Ada and O'Dwyer 2000) and there can be variation between studies in the type of muscle performance measured and the methods used to assess it. This adds an additional limitation to pooling results of studies to show overall effects of RT on muscle performance. Muscular strength is the most common measure conducted in a clinical setting; however muscular endurance and power, while less likely to be assessed (more time consuming and require specialized equipment), are also important. There are four commonly used methods for measuring muscle function. One is computerized dynamometry (i.e. Biodex, Cybex) which is usually used to measure isokinetic strength (torque during constant velocity measured in Nm), endurance and isometric strength. However, the movements are not usually related to skills performed during ADLs and the cost of the equipment can be prohibitive. In addition, one study found that this type of testing was not reliable for measuring peak torque and average peak torque of the affected knee during flexion in people following stroke (Pohl et al. 2000). The second method is the one repetition maximum test (1RM), where the heaviest weight load an individual can lift one time is determined. It is considered a useful measure as it is dynamic and correlates with task performance if the movement of the test is similar to the actual task. However, as with isokinetic computerized dynamometry testing, some patients with hemiparesis may be unable to complete a test due to limited range of motion. The third method is manual muscle testing which grades strength on a scale to a maximum score of 5. It is measured by having an individual apply resistance against gravity or push against resistance by an examiner. Unfortunately the accuracy and sensitivity is relatively low and any variation of 25% or lower cannot be detected by manual muscle testing (Eriksrud and Bohannon 2003). Finally, the
method of hand-held dynamometry has been shown to be sufficient for assessing isometric muscular strength and progress of training (Jones and al. 2007). Moreover, there is high intra and inter-rater reliability when testing is conducted in subjects with neuromuscular disorders. Specifically, reliability and precision of hand-held dynamometer measurements including grip-force has been established for patients with stroke (Eng, Kim and MacIntyre 2002; Bohannon 1990; Hammer and Lindmark 2003). Range of motion does not pose a limitation for isometric assessments, and there are moderate to strong correlations between isokinetic and hand-held dynamometry in neuromuscular disease (Bohannon 1990).

Unfortunately, no commonly agreed standards exist for assessing the effects of an intervention on muscular strength in people following stroke. Development of a common set of assessments would allow data from different studies to be effectively pooled and conclusions drawn that would ultimately help to determine effective training strategies for people following stroke.

1.3.3 Functional Ambulation and Sit-to-stand Performance

Ambulation and sit-to-stand performance are biomechanically demanding activities that are performed every day (Berger et al. 1988). These are crucial activities for resuming independence and are often impaired post-stroke (Lomaglio and Eng 2004; Gresham et al. 1975). Therefore, it is not surprising that the most frequently stated goal by individuals following stroke is to improve ambulation (Bohannon, Andrews and Smith 1988). Ambulatory function can be measured by a number of assessment techniques including preferred and/or fast paced 5-metre, 10-metre, and 22- or 30-foot walking distances (Patterson et al. 2007; Luft et al. 2008; Bohannon and Andrews 2011; Patterson et al. 2010). Also, functional walk tests can include the 6 or 12 minute walk distance assessments (Macko et al. 2005; Patterson et al. 2007; Eng et al. 2003).

A recent meta-analysis comparing AT vs. control and AT+RT vs. control in people post-stroke show both exercise interventions resulted in improvements in ambulatory function as measured by 6 minute walk distance (Brazzelli et al. 2011; Brazzelli et al. 2012). The studies that included individuals who were in the chronic stage of stroke (at least 3 months post-stroke) demonstrated an absolute increase in distance walked ranging from 49.1 metres to 64.6 meters (Macko et al. 2005; Pang et al. 2005) which were significantly greater than demonstrated in control patients.
While meta-analyses comparing AT vs. control and AT+RT vs. control in people post-stroke show both exercise interventions result in significant improvements in ambulatory function (Brazzelli et al. 2011; Brazzelli et al. 2012), few studies have compared these modalities directly. Indeed muscular strength has been positively associated with performance of activities-of-daily-living including walking and sit-to-stand performance (Canning, Ada and O'Dwyer 2000; Morris, Dodd and Meg 2004). This suggests that the RT component may contribute to improved ADL function as RT is predominantly responsible for change in muscular strength (Marzolini, Oh and Brooks 2012; Marzolini et al. 2008; Morris, Dodd and Meg 2004). While AT also contributes to improved functional ambulation through augmented cardiovascular fitness, gait economy, and oxidative capacity of peripheral muscles following stroke (Macko et al. 2005), the effects of AT in stroke recovery might be intensified with the addition of RT. To date, only one study has compared combined AT (cycling) and RT, to AT alone (cycling) in individuals following stroke (Lee et al. 2008). While this study was underpowered with only 12 participants per group, combined training resulted in a greater effect size and two fold greater increase in 6 minute walk distance with combined training (24 meter change, ES=19.6 CI= -1.0 to 40.0) compared to AT alone (12.2 meter change, ES=12.1 CI= -2.9 to 27.1). The smaller absolute change observed in this study compared to others was likely related to the absence of walking as an AT modality (i.e. exercise training on the cycle ergometer was not specific to the outcome measure of functional ambulation).

In contrast to ambulation, few studies have examined the impact of regular physical activity on sit-to-stand performance. Yet, moving from a sitting to standing position is an essential step to initiating ambulation and may be an important barrier to independent mobility for people post-stroke. Moreover, in the older adult population, poor sit-to-stand capacity has been positively associated with increased risk of falls (Buatois et al. 2008). Assessing the amount of time to stand up and sit down for 5 repetitions as quickly as possible from a 43 cm high chair is the most frequently used protocol to assess sit-to-stand performance and has been shown to have good test-retest, and intra- and inter-rater reliability in patients in the chronic stage of stroke recovery (Whitney et al. 2005; Mong, Teo and Ng 2010). Studies examining the effects of exercise
training on sit-to-stand performance have demonstrated conflicting results. A study conducted by Weiss et al., measured the effect of 12 weeks of twice weekly high intensity RT in 7 patients at least 1 year post-stroke on 5 repetition sit-to-stand performance (Weiss et al. 2000). Patients unable to sustain unilateral stance for more than 15 seconds on the affected limb were included in the study. Although there was no control group for comparison, post-study sit-to-stand time improved significantly by a mean of 4.1 seconds (21%, p<0.02). A more recent study conducted by Ouellette et al, randomized 42 individuals, at least 6 months post-stroke with residual lower limb hemiparesis to 12 weeks of either high-intensity RT or a control group of upper extremity stretching. While there were significant improvements in muscular strength, no change in sit-to-stand performance occurred for either the control or RT group. Finally, Globas et al. randomized 38 individuals at least 6 months post-stroke with residual hemiparetic gait to 12 weeks of either AT alone or to usual care (Globas et al. 2012). The results of the timed 5 repetition sit-to-stand test demonstrated a 2.4 seconds improvement in the exercise cohort which was not significantly greater (p=0.1) than the 0.1 second gain observed in the control group. While muscular strength has been positively associated with sit-to-stand performance (Canning, Ada and O'Dwyer 2000; Morris, Dodd and Meg 2004), other factors such as those related to balance, sensation, foot position, and psychological status may be important (Ng 2010; Lord et al. 2002; Akram and McIlroy 2011) and account for these variable results.

1.3.4 Cognition

Most people who survive a stroke will be left with some degree of cognitive impairment that will typically affect domains of attention, executive function and speed of processing (Macko et al. 2005; Ya-Ping et al. 2006). This deficit is of clinical significance as cognitive impairment has been associated with a 3-fold increase in risk for mortality (Hobson and Meara 2009), increased rates of institutionalization (Pasquini et al. 2007), and decreased instrumental activities of daily living function (Mok et al. 2004). While exercise is a promising therapeutic treatment for ameliorating cognitive impairment (Farmer et al. 2004), very few studies have examined the effect of exercise on cognition in people who have had a stroke.

*Effects of Exercise Training on Cognition in People Post-stroke*
Only three studies have examined the effects of an exercise intervention on cognition in people post-stroke. Two studies included an AT intervention and one study included an AT+RT intervention. Rand et al. conducted a single group study that included 11 patients at least 12 months post-stroke with lower-extremity hemiparesis (Rand et al. 2010). The intervention consisted of a 6 month program of AT carried out for 1 hour twice per week, combined with a 1 hour weekly recreation program (socializing and learning new skills such as cooking, bowling, arts and crafts). At the end of the study intervention, there were significant improvements in memory and executive function. Owing to the introduction of two different tasks (AT and recreational activity), the benefits attributed to the exercise intervention are difficult to elucidate.

In a pilot study, Quaney et al. randomized people ≥6 months post-stroke to 8 weeks of either 3 times weekly stationary cycling at 70% maximal heart rate (n=19), or to a non exercise stretching group performed one time per week at home (n=19) (Quaney et al. 2009). Information processing speed was measured by the Serial Reaction Time Task (procedural motor learning) and predictive force accuracy was measured by Predictive Grip Force Modulation assessing conditional learning ability of the relationship between color and weight. Neuropsychological tests included Wisconsin Card Sorting Task measuring rule learning and resistance to perseveration (i.e. the tendency to continue or repeat the rule learned even when inappropriate to the present circumstance), the Stroop test measuring selective attention and conflict resolution, and Trail-Making Tasks A and B measuring executive function. AT failed to improve executive function (compared to control subjects), but resulted in greater gains in motor learning of the non-affected hand. Speed of information processing and predictive force modulation (tests conducted using non-affected hand) improved significantly in the exercise group compared to stretching control group.

Finally, in a single group pilot study Kluding et al. recruited 9 individuals with chronic stroke to participate in a 12-week program of AT and RT, 3 days per week (K luding, Tseng and Billinger 2011). Executive function was measured by the Digit Span Backwards and Flanker tests. Secondary outcome measures included peak oxygen uptake, 6 minute walk distance, 10 metre walk speed, and function by the Fugl-Meyer assessment. After 12 weeks of exercise training there was a significant yet small improvement in working memory (Digit Span Backwards test),
a component of executive function, but no change in the Flanker score. There was also a significant positive correlation between change in aerobic fitness and improved score on the Flanker-incongruent test. This pilot study suggests that participation in AT+RT has an effect on selective measures of executive function and that a greater gain in cardiovascular fitness may be related to greater cognitive benefit.

Only one study has examined the effect of acute exercise on cognition. In a randomized cross-over study, Ploughman et al. examined the effect of acute exercise in 21 people in the chronic stage of stroke (Ploughman et al. 2008). Individuals exercised for 20 minutes on a body-weight-supported treadmill at 70% of estimated heart rate reserve. Immediately following exercise, measures of cognition and an upper-extremity task were completed. Results demonstrated improved movement of the hemiplegic upper extremity (p=0.04) but no change in cognitive performance in immediate recovery when compared to baseline assessments conducted 8 days earlier.

Collectively, the results of these studies suggest that exercise may provide some benefit in ameliorating cognitive decline in people following stroke, with AT+RT interventions providing the most potential for cognitive gain. However, overall the evidence supporting an exercise intervention to improve cognition post-stroke is limited. This may be owing to certain methodological limitations. In the study conducted by Quaney et al., the AT program resulted in only a 5% improvement in \( \text{VO}_{2\text{peak}} \), which the authors attribute to a potentially inadequate intervention duration of 8 weeks. Moreover all studies suffered from a small sample size of patients ranging from a minimum of 9 participants in one study (Kluding, Tseng and Billinger 2011) to 36 individuals randomized to each of two groups in another (Quaney et al. 2009). Two studies were described as pilot studies (Kluding, Tseng and Billinger 2011; Quaney et al. 2009). Another limitation was that only one study included a non-exercising control group (Quaney et al. 2009). The added attention received from a supervised group-based program in the two single group studies may have had a positive effect on cognition. Yet, the study that included a control group required participants to complete once weekly stretching exercises off-site in the patient’s home rather than in the same environment as the exercise group, in part negating the benefit of having a control group (Quaney et al. 2009). The improvements in speed of
information processing and predictive force modulation reported by Quaney et al. and improved movement of the hemiplegic upper extremity reported by Ploughman et al., while promising, are predominantly related to motor function change rather than higher level cognitive change. Large randomized controlled studies are required before a strong case can be made for exercise to be used to target cognitive impairment in people following stroke.

**Type of Exercise and Effect on Cognition**

**Indirect Evidence for Exercise Related Benefit**

Cardiopulmonary fitness has been extensively studied as a possible mediator of cognitive performance (Swardfager et al. 2010). Kluding et al., reported a correlation between improved $\dot{VO}_{2\text{peak}}$ and improved executive control on the Flanker test in individuals post-stroke participating in AT+RT (Kluding, Tseng and Billinger 2011). This was the only study to examine this association in patients following stroke. In contrast, an earlier meta-analysis and a systematic review of 10 and 11 studies respectively, did not substantiate an association between changes in $\dot{VO}_{2\text{peak}}$ and change in cognitive function (Angevaren et al. 2008; Etnier et al. 2006). This may be owing to factors that limit individuals in reaching a “true” $\dot{VO}_{2\text{max}}$ such as lack of motivation, depressive symptoms (Lavoie et al. 2004), and musculoskeletal issues which may reduce the utility of the actual $\dot{VO}_{2\text{peak}}$ as a measure of cardiopulmonary fitness. Nevertheless, finding ways to optimize cardiovascular fitness may have important implications for cognitive outcomes.

Compared to cardiovascular fitness, there is little indirect evidence to suggest that body composition mediates cognitive function. Nevertheless, cross sectional studies provide insight into the possible benefit of RT for cognitive performance. In a large cross sectional study of 7,000 older healthy women, Nourshshemi et al., measured cognition and body composition by dual energy x-ray absorptiometry (DXA) (Nourhashemi et al. 2002). Results demonstrated that women in the lowest quartile of muscle mass had a significantly greater odds ratio for cognitive impairment compared with those in the highest quartile of muscle mass (OR 1.43, 95% CI=1.07-
Subsequent to this study, a cross-sectional case-control study conducted by Burns and colleagues examined the association of body composition (measured by DXA) with cognition and brain volume in individuals with early-stage Alzheimer disease (n=70) and in those without dementia (n=70) (Burns et al. 2010). Magnetic resonance imaging and neuropsychological testing were conducted for each participant. Results revealed that whole-brain volume, white matter volume, and global cognitive performance all demonstrated a significant positive association with lean mass when controlling for age and sex. Collectively, these data suggest that an RT exercise program, with its anabolic component (Marzolini, Oh and Brooks 2012; Marzolini et al. 2008), has the potential to ameliorate cognitive deficits. However, randomized studies are required to determine causality.

**Resistance Training Exercise and Effects on Cognition**

While many studies have investigated the association between aerobic exercise and cognition, very few studies have examined the effects of an RT intervention in healthy adults. In a single-blinded randomized trial conducted by Liu-Ambrose et al., 155 community-dwelling senior women were randomized to 12 months of either once weekly (n=54) or twice-weekly (n=52) RT or twice-weekly balance and tone training (control) (n=49) (Liu-Ambrose et al. 2010). The study demonstrated that both once weekly and twice weekly RT resulted in significantly greater improvements post-intervention (12 months) in parameters of executive cognitive function, including selective attention and conflict resolution (Stroop test) compared to the control group. There were no significant improvements in any parameter of cognition at the mid point of the study (6 months).

In another study to examine the impact of RT on cognitive function, Cassilhas et al. randomized 62 elderly individuals to 24 weeks of either moderate intensity RT at 50% of 1 RM (n=19), high intensity RT at 80% of 1RM (n=20), or a control group of stretching exercises (n=23) (Cassilhas et al. 2007). Lean muscle mass measured by BOD POD-air displacement method, increased significantly only in the high intensity group compared to control. Both experimental RT groups demonstrated greater improvement than control in cognitive performance (tests designed to measure short- and long-term memory), with better central executive functioning, attention and
lower neglect. There were no differences in change in cognitive function between high and low intensity RT groups. In addition, change in serum insulin-like growth factor-I (IGF-1) was significantly higher for RT groups (low intensity and high intensity) compared to control (p=0.02 and p<0.001 respectively) and two-fold higher in the high intensity than lower intensity group (p=0.15). IGF-1 has been reported to be a mediator between exercise and neurocognitive change (Aberg, Brywe and Isgaard 2006).

Collectively, the studies by Liu-Ambrose and Cassilhas suggest that either once or twice weekly RT and either high or low intensity RT result in cognitive benefit. Greater gains in muscle power or muscle mass did not appear to be a mediator of cognitive change in these studies. The time-course of improvement was shorter for the study by Cassilhas et al. with significant improvements in cognition occurring after 6 months. This was in contrast to the study by Liu-Ambrose et al., where improvements only occurred after 12 months of training and not at 6 months. This may be related to sex difference between studies, or the greater training frequency adopted by Cassilhas et al. compared to Liu-Ambrose et al. (3 times weekly training vs. 2 times weekly).

**Possible Mechanisms for Change in Cognition**

There are a number of ways that exercise has been hypothesized to have an effect on cognition. The findings of the greater efficacy of the “combined training” (AT +RT) approach for improving cognition when compared to an AT only intervention reported in meta-analyses (Colcombe and Dramer 2003; Smith et al. 2010) may help to elucidate causal pathways. The meta analytic findings are consistent with mechanistic studies demonstrating that while AT augments cerebral vascular blood flow post-stroke (Ivey et al. 2011) and brain-derived neurotrophic factor (BDNF) (Ploughman et al. 2005), RT may mitigate cognitive impairment through a reduction in serum homocysteine (Vincent et al. 2003) and increased concentrations of IGF-I (Borst et al. 2001); an intermediary of BDNF. Neurotrophins such as BDNF and IGF-I are proteins that support neuroplasticity by signaling neurons to survive, grow, or differentiate (Johnston 2009; Hennigan, O’Callaghan and Kelly 2007). IGF-1 concentrations have been shown to increase following RT programming (Cassilhas et al. 2007; Borst et al. 2001) and have
been implicated as a mediator of cognitive improvement. Studies in animal models have shown that exercise facilitates IGF-1 to enter the hippocampus, increasing neuronal activity, neurogenesis, and spine growth (Trejo, Carro and Torres-Aleman 2001; Chang et al. 2011). It provides a neuroprotective effect for both white and gray matter and there is a strong indication that IGF-1 can stimulate the regeneration of neural tissue (Kooijman et al. 2009) however the time line for a measurable change is not known. Several studies conducted in individuals following stroke have demonstrated that higher levels of circulating IGF-1 are associated with better long-term functional outcomes (Åberg et al. 2011; Bondanelli et al. 2006). However, while RT may increase IGF-1 concentrations, the optimal dose of RT to increase IGF-1 is not known. A study conducted by Borst and colleagues, examined the effect of the number of RT sets prescribed on IGF-1 in a group of 37 healthy men and women (mean age 37 years). Individuals were randomized to 24 weeks of either 1 set of RT or 3 sets of RT exercises. While both interventions resulted in a significant increase in serum IGF-1 levels (no further increase between week 13 and 25), there was no between group difference (Borst et al. 2001).

Another potential mechanism for RT related improvement in cognition is the reduction of serum homocysteine levels. Elevated homocysteine levels are neurotoxic in rat models (Kruman et al. 2000) and associated with cognitive impairment, Alzheimer’s diseases, and cerebral white matter lesions (Schafer et al. 2005; Seshadri et al. 2002). Homocysteine levels have been shown to decrease following RT programming with no difference in the magnitude of change between high and low intensity RT (50 vs. 80% of 1 repetition maximum) (Vincent et al. 2003).

While RT may augment brain function by increasing serum IGF-1 and reducing serum homocysteine concentrations, AT may facilitate brain health by augmenting cerebral vascular blood flow post-stroke (Ivey et al. 2011) and upregulating BDNF (Ploughman et al. 2005). Pre-clinical studies have provided strong evidence that AT increases cerebral blood flow in animals (Rhyu et al. 2010; Endres et al. 2003; Gertz et al. 2006). This is of clinical significance as reduction in cerebral blood flow or cerebral vasomotor reactivity has been linked to cognitive decline (Vicenzini et al. 2007). A recent study conducted in humans has provided the first evidence that AT can induce cerebral vasomotor reactivity in people following stroke with hemiparesis (Ivey et al. 2011). Also, there is compelling evidence from pre-clinical research
trials that AT upregulates BDNF, which is one of the key neurotrophins that mediates synaptic plasticity in the hippocampus of the brain (Vicario-Abejon et al. 1998). When BDNF is infused into the hippocampal neurons of the rat brain, synaptic signaling is immediately enhanced (Knaepen et al. 2010). Ploughman et al., in a well designed pre-clinical study, demonstrated the role of BDNF in functional recovery related to rehabilitation (Ploughman et al. 2009). Following middle cerebral artery occlusion, rats were stratified according to impairment and randomly infused with either Antisense BDNF oligonucleotide (blocking the expression of BDNF) or a saline solution. The animals were further randomized to receive either a rehabilitation program of running and skilled reaching training or no rehabilitation. The animals infused with the BDNF blocking agent had no improvement in skilled reaching. The untreated rehabilitation group exhibited significantly greater improvement in skilled reaching ability in the contralateral limb than the other groups over time. Therefore, when BDNF is blocked, the animals show impairments in learning and memory. Similarly, research conducted in healthy individuals who have a Val66Met polymorphism in the BDNF gene (blocking BDNF efficacy), demonstrated an attenuated ability to change cortical maps in response to motor learning (Kleim et al. 2006). The existence of an exercise threshold to increase BDNF, or the frequency, intensity or duration of exercise required to optimize brain plasticity through BDNF mobilization has not been elucidated.

A systematic review of 24 randomized, non randomized, and retrospective studies examining the effects of acute and chronic exercise on BDNF in healthy individuals and those with chronic disease was conducted by Knaepen et al. (Knaepen et al. 2010). Most of the studies examining the acute response to AT in healthy individuals and those with chronic disease (69% and 86% of studies respectively) showed an immediate increase in BDNF that quickly returned to baseline levels in recovery. In contrast, none of the studies (n=2) examining the acute response to RT showed a change in serum BDNF levels in immediate recovery. Examination of chronic effects of exercise training revealed that only 30% of AT or RT training studies (3/10 studies) showed an increase in basal serum BDNF levels following training. However, the studies incorporating an RT intervention were of short duration (5-12 weeks).
Research examining the effect of exercise on BDNF poses many challenges. It is reported that approximately 25% of humans have the polymorphism Val66Met that blocks BDNF efficacy (Kleim et al. 2006) and is rarely accounted for in studies. Also, three retrospective observational studies demonstrated that highly trained people exhibit paradoxically lower levels of basal serum BDNF than either untrained, moderately trained or low cardiorespiratory fit healthy individuals (Knaepen et al. 2010). It has been posited that lower levels of BDNF in trained individuals are due to a more effective clearance rate than in non trained individuals, resulting in faster uptake in the brain with less BDNF circulating in the periphery (Knaepen et al. 2010). Serum BDNF levels may be altered initially, triggering downstream signaling cascades important for behavioral changes, but return to baseline by the end of the intervention. Others suggest that lower concentrations of BDNF may be due to the increase in plasma volume (mean change of 12% in 8 days but can range from 10-20%) (Convertino et al. 1980) most of which occurs in the first 2 to 4 weeks after initiation of an exercise training program. In addition, serum basal levels of BDNF can fluctuate between 1.5 to 30.9 ng/mL and plasma levels can fluctuate even more. Both can be influenced by diurnal fluctuations, fitness, age, sex, body weight, nutrition and neurological, immunological or metabolic disorders (Lommatzsch, Zingler and Schuhbaeck 2005). Finally, methodological issues related to blood analyses can interfere with accurate measurements. For example, platelets in plasma concentrations may be activated to release BDNF by the type of anticoagulant used in the test tubes which may increase variability between studies.

1.3.5 Effect of Early and Late Interventions on Physiological Outcomes:

Unfortunately, there is a dearth of studies comparing exercise interventions introduced early in the chronic recovery period compared to late in recovery in people following stroke. These types of studies would provide insight into establishing more effective timing of exercise interventions, especially in the chronic post-stroke phase of recovery (>3 months post-stroke). A recent study conducted by Duncan et al. known as the LEAPS study, stratified 408 patients with hemiparesis by walking ability and randomized them to 12-16 weeks of body-weight support treadmill training either 2 months or 6 months following stroke (Duncan et al. 2011) or to a control
intervention that included strength and balance exercise provided by a physical therapist in the home two months following stroke. Measures were conducted at baseline, and then at 6 months and 12 months later. While the early intervention group (intervention at 2 months post-stroke) had accelerated improvements at 6 months in six minute walk distance and functional outcomes when compared to the later intervention group (intervention at 6 months post-stroke), at one year post-stroke, there was no significant difference in the proportion of patients who improved walking function between those randomized to either of the body-weight supported treadmill groups or to the control group. The failure of the aerobic exercise intervention to result in greater ambulatory benefit than control at 1 year may be related to exercise training methodological issues. All patients were required to walk at a fixed velocity (3.2 km/hr) for 20 to 30 minutes followed by 15 minutes of progressive overground walking. Exercise prescription parameters, especially intensity, were not tailored to the functional capacity of the individual as a CPET was not conducted at baseline. Moreover, exercise training principles suggest that for any improvement to occur, a gradual progression of frequency, intensity, or duration must occur. The description in the methods section indicates that the treadmill speed was fixed throughout the training program at 3.2 km/hr. There was no description of how the overground walking prescription was progressed. Moreover, the transition from supervised exercise performed on equipment likely not available to individuals outside of the study environment, to unsupervised training in the community was not described. This is important as unsupervised exercise was carried out for as long as 10 months in the earlier intervention group before the final assessment. This period of inactivity would mitigate the accelerated recovery in the earlier intervention group when measured remote from the cessation of the supervised intervention. These results demonstrate that an intervention introduced earlier in the stroke recovery process results in an accelerated rate of change but no difference 6 to 10 months from the time of the intervention. Future studies are needed to examine the effect of exercise interventions introduced in the earlier and later chronic stage of stroke that include adequate transition to home-based exercise. This is of particular importance for participants of adapted CR programs who are typically referred at least 3 months to more than 5 years following the stroke event (Lennon et al. 2008; Marzolini et al. 'The Feasibility of Cardiopulmonary Exercise Testing for Prescribing Exercise to People after Stroke' 2012; Tang et al. 2010). Determining if greater benefits are to be derived from referring
patients earlier after stroke (i.e. within 1 year) will be important in establishing best practice guidelines. Further research is required to elucidate the underlying causal pathways leading to change in chronic stroke recovery, i.e. restitution of underlying deficits vs. adoption of behavioral compensation strategies.

1.4 Research Objectives and Hypotheses

The focus of this body of work is to add to the existing literature examining the feasibility and efficacy of CR programs for people following stroke. Identified in the review of literature are issues related to both the long-term chronic effects and acute physiological response to exercise that has not been previously examined within a CR setting. Addressing these gaps in the literature will provide further support for the integration of more effective CR programs for the care of people recovering from stroke.

Therefore, the specific objectives of the 4 studies were the following:

Objective 1:

Examining the utility of the CPET for developing an exercise prescription for patients ≥3 months post-stroke with motor impairments conducted at baseline and after 6 months of exercise training.

To determine the proportion of patients who achieved either $\text{VO}_{2\text{max}}$, VAT, or a clinically relevant abnormality on the baseline and 6 month CPETs

Hypothesis 1:

Most patients (>50%) will reach a level of exertion that would provide information for exercise prescription with no serious cardiovascular events (death, myocardial infarction, or sustained ventricular tachycardia).

Objective 2:
Assessing the ability of patients following stroke to achieve recommended exercise levels during a single 60 minute exercise session of AT (30 minutes) and RT (30 minutes).

a. To measure resting metabolic rate and oxygen uptake during 60 minutes of AT and RT by ambulatory oxygen monitor and compare obtained values to recommended minimal levels i.e., ≥20 minutes of exercise at ≥40% of $\dot{V}O_{2\text{peak}}$, ≥30 minutes of exercise at ≥3 METs, and an energy expenditure of approximately 200 kcal-session\textsuperscript{-1}.

Hypothesis 2:
It was hypothesized that the acute exercise oxygen uptake measured during a standard 60 minute AT and RT session would reach the minimal intensity recommendation of 40% of $\dot{V}O_{2\text{peak}}$ for a duration of at least 20 minutes.

Objective 3:
Evaluating the effects of a 24 week adapted CR program of RT and AT on physiological parameters and to examine the effect of stroke recovery time on change in outcome variables.

Hypothesis 3:
It was hypothesized that a 6-month CR program would result in significant improvements in the primary outcome measures of ambulatory function, paretic-side leg extension strength, timed sit-to-stand performance, and $\dot{V}O_{2\text{peak}}$ independent of time from stroke to commencement of the exercise program.

Objective 4:
Evaluating the effects of a 6 month exercise program of RT+AT on cognitive function

a. To explore associations between change in cognition score and change in physiological outcomes attributed to AT (cardiovascular fitness) and RT (muscle mass accretion).
Hypothesis 4:

It was hypothesized that 6 months of AT+RT would result in a significant improvement in cognition and be positively associated with favorable change in submaximal cardiovascular fitness and fat-free mass.
Chapter 2  THE FEASIBILITY OF CARDIOPULMONARY EXERCISE TESTING FOR PRESCRIBING EXERCISE TO PEOPLE FOLLOWING STROKE

Published in Stroke (Marzolini, S., P.I. Oh, W. McIlroy, and D. Brooks, Stroke, 43, 1075-81, 2012)

Susan Marzolini was Case Manager for the patients following stroke of this study and prescribed the aerobic and resistance training components as well as progression of exercise to each patient. Susan Marzolini also conceived and designed the research with Dr. Brooks, extracted, analysed and interpreted the data, performed statistical analysis and drafted the manuscript.

2.1 ABSTRACT

Background and Purpose: Despite the importance of exercise training in mitigating cardiovascular risk, the development of exercise programs for people post-stroke has been limited by lack of feasibility data concerning cardiopulmonary exercise testing (CPET) to inform the exercise prescription. Therefore, we examined the feasibility of CPETs for developing an exercise prescription in people≥3 months post-stroke.

Methods: CPET results from 98 consecutively enrolled patients post-stroke with motor impairments and 98 age-and sex-matched patients with coronary artery disease (CAD) were examined at baseline and after 6 months of exercise training.

Results: The proportion of patients with stroke and CAD attaining an intensity sufficient for prescribing exercise at baseline was 68.4% vs. 82.7% respectively (p=0.02) and 84.7% vs. 83.8% (p=0.9) at 6 months. Women were less likely than men post-stroke to achieve a sufficient intensity at baseline (40% vs. 80.9%, p<0.001) but not at 6 months (78.3% vs. 87.1, p=0.3). A clinically relevant abnormality (CRA) occurred in 11.2% of stroke and 12.2% of CAD patients
on baseline CPETs (p=0.8) and 10.6% of stroke and 5.9% of CAD patients on the 6 month CPET (p=0.4). No serious cardiovascular events occurred during 349 CPETs.

**Conclusions:** Most patients following stroke achieved a level of exertion during the CPET sufficient to inform an exercise prescription. At least 1/10 patients post-stroke developed a CRA on baseline and post-program CPETs with no serious cardiovascular events. These data support the feasibility and safety of CPETs for prescribing exercise post-stroke. Strategies to improve utility of baseline CPETs for women post-stroke require further investigation.
2.2 Introduction

Despite exercise being an important component of stroke rehabilitation, there is a dearth of information on the clinical utility and feasibility of cardiopulmonary exercise testing (CPET) for individuals with a history of stroke prior to engaging in exercise. This issue merits special attention in view of the growing recognition of the importance of exercise in the secondary prevention of stroke and the risk of comorbid coronary artery disease (CAD).

CPETs are not routinely administered prior to starting a cardiac rehabilitation (CR) program following stroke (Gitter and Halar 1995). Consequently, exercise is often prescribed without an objective assessment of the patients’ functional capacity, resting and exercise blood pressures, exercise related symptoms, and/or electrocardiogram (ECG) changes including dysrhythmias (Stone et al. 2009). Despite recommendations to base exercise prescriptions on CPET results, few data are available to substantiate the feasibility and safety of graded exercise tests with ECG monitoring following stroke (Gordon et al. 2004). Lacking this information has hindered the development of exercise programs tailored to the functional capacities of survivors of stroke.

A CPET involves measuring oxygen uptake, carbon dioxide output and minute ventilation, while monitoring blood pressure, and 12-lead ECG. Measures derived from the CPET guide the activity attributes of the exercise prescription. From both a safety and efficacy point-of-view, the most important parameter of the prescription is that of intensity (Rimmer et al. 2009; Kavanagh et al. 2002; Gormley et al. 2008). Intensity of exercise is believed to be the primary factor responsible for change in peak oxygen uptake (\(VO_{2\text{peak}}\)) (Lam et al. 2010; Gormley et al. 2008) and a higher \(VO_{2\text{peak}}\) is associated with lower stroke risk in males (Kurl et al. 2003), as well as lower mortality in cardiac patients (Kavanagh et al. 2002). Moreover, evidence that the intensity of physical activity (moderate to high) may be a greater determinant of stroke prevention than duration of exercise is accumulating (Willey et al. 2009; Lee, Folsom and Blair 2003).
In view of the importance of exercise intensity, an exercise prescription based on objective measures derived from a CPET is important. The CPET determines the ventilatory anaerobic threshold (VAT) which represents the movement from aerobic to anaerobic metabolism (Wasserman et al. 1973) and is recommended as an appropriate target intensity level for the prescription of exercise (Gordon and Scott 1995; Dwyer 1994; Tabet et al. 2006). Achievement of maximal oxygen uptake (\(\dot{V}O_2^{\text{max}}\)) (i.e. an individual’s maximal capacity to transport and use oxygen) is another important measure used to prescribe exercise intensity. Therefore, \(\dot{V}O_2^{\text{max}}\), VAT and the level at which a clinically relevant abnormality (CRA) occurs are all critical measures for prescribing an exercise intensity that is both safe and effective. However, people who have had a stroke may be limited by a constellation of motor and neurological impairments that may prevent them from reaching these critical levels. These issues may discourage the systematic application of CPETs for individuals following stroke.

Accordingly, the objective of this study was to examine the feasibility of the CPET for developing an exercise prescription for chronic stroke patients (\(\geq 3\) months post-stroke with no upper limit) with motor impairments. We hypothesized that most patients (>50%) would reach a level of exertion that would provide information for exercise prescription with no serious cardiovascular events (death, myocardial infarction, or sustained ventricular tachycardia).

### 2.3 Methods

This was a retrospective analysis of CPETs conducted at baseline and after 6 months of exercise training in 98 consecutively enrolled patients in Toronto Rehabilitation Institution’s Risk Factor Modification and Exercise Program following Stroke (TRI-REPS) (Figure 2.1). The TRI-REPS program is a substream of the CR program, modeled after the traditional CR program. A comparison group of 98 age- and sex-matched patients consecutively enrolled in the CR program who had a documented history of CAD and no prior history of stroke or transient ischemic attack were included. Patients in both cardiac and stroke services attended 90-minute exercise classes once per week for 6 months and were offered baseline and follow up (6 month) CPETs. To test our hypothesis, we calculated the proportion of patients who achieved either \(\dot{V}O_2^{\text{max}}\), VAT, or a
CRA that would prohibit an exercise prescription beyond the intensity where it occurred, on the baseline and 6 month CPETs.

**Figure 2.1 Flow Diagram**

![Flow Diagram](image)

**AT** = Aerobic Training

**RT** = Resistance Training

### 2.3.1 Subjects

To be admitted to the TRI-REPS program, patients had to be $\geq 3$ months post-stroke (no upper limit) with a stroke-related motor impairment score $< 7$ on the Chedoke-McMaster Stroke Assessment scale (CMSA) of the arm, hand, leg, or foot (described below). In addition, patients had to be able to ambulate $\geq 10$ metres independently with/without an assistive device with no significant limitations due to pain, and no contraindications to maximal exercise testing (ACSM 2009) such as a recent significant change in the resting ECG, symptomatic severe aortic stenosis,
uncontrolled resting severe hypertension, or uncontrolled metabolic disease such as diabetes. Higher functioning patients were integrated into the regular CR program and were not included in the analysis. Patients in the CAD cohort, had a documented history of CAD (myocardial infarction, angiographic evidence showing ≥50% stenosis in ≥1 major coronary artery, percutaneous coronary intervention (PCI), or coronary artery bypass graft surgery (CABG) and were referred ≥6 weeks since CABG or myocardial infarction or ≥3 weeks since PCI. The study was approved by the institution’s Research Ethics Board.

2.3.2 Post-stroke Baseline Assessments

Motor recovery stage of the arm, hand, leg and foot of the stroke-affected side was classified on the 7 point CMSA scale (Gowland et al. 1993). A CMSA motor impairment score of 1 indicates flaccid paralysis, 3 describes marked spasticity and weakness, 6 indicates near normal coordination of patterns of movement and no spasticity, and 7 describes normal movement (Gowland et al. 1993). Patients performed the 6 minute walk test (ATS 2002) walking as far as possible over a 30-meter course in 6 minutes.

2.3.3 Baseline Characteristics

At entry to CR, individuals post-stroke had a similar cardiovascular risk factor profile when compared to CAD patients (Table 2.1). Fewer stroke than CAD patients were prescribed β-blockade medications (p <0.001). Most individuals after stroke had a history of ischemic stroke (70.4%), used a gait aide for ambulation (59.2%), and 93.9% had a motor impairment score between 3 (marked spasticity) and 6 (near normal coordination of movement) of the leg on the 7-point CMSA scale (Table 2.2). Six minute walk test distance at baseline represented 52.3±27% of predicted norms (Enright and Sherrill 1998).
<table>
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<th>Characteristics</th>
<th>CAD n=98</th>
<th>Stroke n=98</th>
<th>Men n=68</th>
<th>Women n=30</th>
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<tbody>
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<td>68 (69.4)</td>
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<tr>
<td>Age yrs. (range)</td>
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<td>Waist Circumference, cm</td>
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<td>98.4±12.4</td>
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<td>31 (31.6)†</td>
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<td>4 (18.2)</td>
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<td>5 (22.7)</td>
<td>1 (11.1)</td>
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<td>4 (18.2)</td>
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<td>94.9±201.6</td>
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<td>40(41.7)/4(4.1)</td>
<td>29(43.3)/2(6.9)</td>
<td>11(37.9)/2(2.9)</td>
</tr>
<tr>
<td>Chronic Obstructive Lung Disease</td>
<td>12(12.6)</td>
<td>13(13.4)</td>
<td>8(11.8)</td>
<td>5(17.2)</td>
</tr>
<tr>
<td>Thyroid Disease</td>
<td>13(13.7)</td>
<td>5(5.2)*</td>
<td>2(10.3)</td>
<td>3(10.3)</td>
</tr>
<tr>
<td>Depression Requiring Medication</td>
<td>9(9.4)</td>
<td>23(24.5)*</td>
<td>18(27.3)</td>
<td>5(17.9)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------</td>
<td>-----------</td>
<td>-----------</td>
<td>--------</td>
</tr>
<tr>
<td>No Significant Physical Activity Prior to Event (&lt;30 minutes, 3x/wk), n(%)</td>
<td>64(66.7)</td>
<td>74(78.7)*</td>
<td>56(86.2)</td>
<td>18(62.1)*</td>
</tr>
<tr>
<td>Medications, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ß-blockers</td>
<td>79(80.6)</td>
<td>42(42.9)†</td>
<td>29(42.6)</td>
<td>13(43.3)</td>
</tr>
<tr>
<td>Ca^{2+}-channel antagonists</td>
<td>14(14.3)</td>
<td>27(27.6)*</td>
<td>20(29.4)</td>
<td>7(23.3)</td>
</tr>
<tr>
<td>Other Antihypertensives</td>
<td>81(82.7)</td>
<td>69(70.4)</td>
<td>46(67.6)</td>
<td>23(76.7)</td>
</tr>
<tr>
<td>Lipid lowering agents</td>
<td>91(92.9)</td>
<td>80(81.6)*</td>
<td>55(80.9)</td>
<td>25(83.3)</td>
</tr>
<tr>
<td>No 6 Month CPET, n (%)</td>
<td>30 (30.6)</td>
<td>13 (13.3)†</td>
<td>6 (8.8)</td>
<td>7 (23.3)</td>
</tr>
</tbody>
</table>

Values are mean ± SD unless otherwise indicated

*p=<0.05 and †p=<0.001 between CAD and Stroke or between Women and Men post-stroke

CAD=coronary artery disease, PCI= Percutaneous coronary intervention, CABG= Coronary Artery Bypass Graft
Table 2.2 Additional Characteristics of People After Stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=98</td>
<td>n=68</td>
<td>n=30</td>
</tr>
<tr>
<td></td>
<td>N(%) or Mean±SD (Range)</td>
<td>N(%) or Mean±SD (Range)</td>
<td>N(%) or Mean±SD (Range)</td>
</tr>
<tr>
<td>I/H/U Stroke Type</td>
<td>69(70.4)/27(27.6)/2(2)</td>
<td>48(70.6)/19(27.9)/1(1.5)</td>
<td>21(70.0)/8(26.7)/1(3.3)</td>
</tr>
<tr>
<td>Left/Right/Bilateral Hemisphere Affected</td>
<td>54(55.1)/41(41.8)/3(3.1)</td>
<td>37(54.4)/30(44.1)/1(1.5)</td>
<td>17(56.7)/11(36.7)/2(6.7)</td>
</tr>
<tr>
<td>Diabetes and/or CAD</td>
<td>50 (51)</td>
<td>32 (47.1)</td>
<td>18 (60)</td>
</tr>
<tr>
<td>Gait Aids, N/C/R/WC</td>
<td>40(41)/33(34)/22(22)/3(3)</td>
<td>26(38.2)/27(39.7)/13(19)/2(3)</td>
<td>14(46.7)/6 (20)/9(30)/1(3.3)</td>
</tr>
<tr>
<td>CMSA Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm/Hand</td>
<td>4.2±1.6(1-7)/4.4±1.9(1-7)</td>
<td>4.0±1.6(1-7)/4.2±2.0(1-7)</td>
<td>4.7±1.6(2-7)/4.9±1.9(1-7)</td>
</tr>
<tr>
<td>Leg/Foot</td>
<td>5.0±1.1(3-7)/4.2±1.6(1-7)</td>
<td>4.8±1.1(3-7)/3.8±1.5(1-7)</td>
<td>5.5±0.9(4-7)<em>/4.9±1.6(2-7)</em></td>
</tr>
<tr>
<td>Six Minute Walk Distance, metres</td>
<td>271.6±139 (17-590)</td>
<td>256.1±139 (17-576)</td>
<td>310±137.9 (67-590)</td>
</tr>
<tr>
<td>% of age, height, weight, sex predicted norm</td>
<td>52±26.8 (3-119)</td>
<td>48.7±25.8 (3-117)</td>
<td>59.9±28.2(17-119)</td>
</tr>
<tr>
<td>Type of Exercise Prescribed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W/W+C</td>
<td>43(43.8)/35(35.7)</td>
<td>30(44.1)/26(38.2)</td>
<td>13(43.3)/9(30)</td>
</tr>
<tr>
<td>C/W+E or S</td>
<td>9(9.2)/5(5)</td>
<td>7(10.3)/2(2.9)</td>
<td>2(6.7)/2(6.7)</td>
</tr>
</tbody>
</table>

*p=<0.05 between women and men,
I=Ischemic, H=Hemorrhagic, U=Unknown, N=None, C=Cane, R=Rollator, WC=Wheel Chair, CMSA=Chedoke-McMaster Stroke Assessment, W=walk only; W+C=walk and cycle combination; W + E or S = walk and either elliptical or swim combination
CPETs were conducted in 98 stroke and 98 CAD patients at baseline and 85 stroke and 68 CAD patients after 6 months of training. A greater proportion of patients in the CAD cohort discontinued the CR program than in the stroke cohort (30% vs. 13%, p=0.001). Most baseline CPETs were conducted on the upright cycle for CAD patients (78.6%) and on the recumbent cycle for individuals following stroke (50%) (Table 2.3).
2.3 Cardiopulmonary Exercise Test Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAD N=98</td>
<td>Stroke N=98</td>
</tr>
<tr>
<td></td>
<td>CAD N=68</td>
<td>Stroke N=85</td>
</tr>
<tr>
<td><strong>Mode of Testing, n (%)</strong></td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>Upright/Recumbent Cycle</td>
<td>77(78.6)/3(3.1)</td>
<td>43(43.9)/49(50)</td>
</tr>
<tr>
<td></td>
<td>47(69.1)/0(0)</td>
<td>42(49.4)/35(41.2)</td>
</tr>
<tr>
<td>Treadmill</td>
<td>18(18.4)</td>
<td>6(6.1)</td>
</tr>
<tr>
<td></td>
<td>19(27.9)</td>
<td>8(9.4)</td>
</tr>
<tr>
<td><strong>VO_{2peak}, mL·kg^{-1}·min^{-1}</strong></td>
<td>19.3±6.3</td>
<td>15.1±4.6†</td>
</tr>
<tr>
<td></td>
<td>22.0±7.9</td>
<td>17.7±4.7†</td>
</tr>
<tr>
<td><strong>VO_{2peak}, % Age and Gender Predicted Norms</strong></td>
<td>79.2±22.4</td>
<td>63.1±25.7†</td>
</tr>
<tr>
<td></td>
<td>92.7±25.6</td>
<td>75.6±27.6†</td>
</tr>
<tr>
<td>VAT, mL·kg^{-1}·min^{-1}</td>
<td>15.9±4.6</td>
<td>13.2±3.5†</td>
</tr>
<tr>
<td></td>
<td>18.5±5.5</td>
<td>14.2±3.4†</td>
</tr>
<tr>
<td>VAT, % of VO_{2peak}</td>
<td>77.8±9.7</td>
<td>79.1±9.6</td>
</tr>
<tr>
<td></td>
<td>77.0±8.6</td>
<td>78.4±9.4</td>
</tr>
<tr>
<td>Peak Respiratory Exchange Ratio</td>
<td>1.14±0.11</td>
<td>1.08±0.14*</td>
</tr>
<tr>
<td></td>
<td>1.15±0.11</td>
<td>1.11±0.12</td>
</tr>
<tr>
<td>% Predicted Max HR Achieved on CPET</td>
<td>94.0±16</td>
<td>79.7±15.8†</td>
</tr>
<tr>
<td></td>
<td>98±14.8</td>
<td>85.5±17.5†</td>
</tr>
<tr>
<td>≥85% Predicted Maximal Heart Rate, n (%)</td>
<td>72(73.5)</td>
<td>36(36.7)†</td>
</tr>
<tr>
<td></td>
<td>53(77.9)</td>
<td>36(42.4)†</td>
</tr>
<tr>
<td>Symptoms Reported During CPET</td>
<td>15(15.3)</td>
<td>6(6.1)</td>
</tr>
<tr>
<td></td>
<td>4(5.9)</td>
<td>5(5.9)</td>
</tr>
<tr>
<td>Dyspnea, n (%)</td>
<td>10(10.2)</td>
<td>4(4.1)</td>
</tr>
<tr>
<td></td>
<td>2(2.9)</td>
<td>5(5.9)</td>
</tr>
<tr>
<td>Chest Discomfort, n (%)</td>
<td>4(4.1)</td>
<td>0(0)</td>
</tr>
<tr>
<td></td>
<td>2(2.9)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Dizziness, n (%)</td>
<td>1(1)</td>
<td>2(2)</td>
</tr>
<tr>
<td></td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Left Ventricular Hypertrophy</td>
<td>3(3.1)</td>
<td>12(12.2)*</td>
</tr>
<tr>
<td>Cornell Criteria, n (%)</td>
<td>2(2.9)</td>
<td>12(14.1)*</td>
</tr>
</tbody>
</table>

Values are mean±SD unless otherwise indicated
CAD=coronary artery disease, $\dot{V}O_{2\text{peak}}$ =peak oxygen uptake, VAT=ventilatory anaerobic threshold
*p=<0.05 and †p=<0.001 between CAD and Stroke

2.3.4 Cardiopulmonary Exercise Test

CPETs were conducted in all patients at baseline and 6 month except in those who prematurely discontinued the CR program. A resting 12-lead ECG, medical history, and anthropometric measures were collected prior to each CPET. The test was conducted by two cardiopulmonary exercise technicians under the direct supervision of one physician. A CPET on either a recumbent cycle ergometer with specialized pedals to secure feet (Ergoline Select 1000, Germany) or upright cycle (Ergoselect 200P, Germany), or a treadmill was performed. The type of ergometer and testing protocol was chosen by the testing staff based on balance, and control of leg/foot position in the pedal. None of the testing modalities required exertion of the upper body. Individuals post-stroke who had excessive hemiparetic hip weakness had their leg stabilized by an elastic band looped around the thighs. Work load was increased by either 8.3 or 16.7 Watts every minute at a pedaling rate of 60 RPM, the aim being to achieve test durations of between 8-12 minutes. Breath-by-breath gas samples were collected and averaged over a 20 second period via calibrated metabolic cart (SensorMedics Vmax Encore, California) with continuous monitoring of 12-lead ECG (Marquette Case 80), and blood pressure. Indications for discontinuing CPET were peak volitional effort (i.e. if the patient was unable to maintain the required pedaling rate), the appearance of adverse clinical signs or symptoms as described elsewhere (ACSM 2009), or if the patient achieved $\dot{V}O_{2\text{max}}$ (described below). The expected $\dot{V}O_{2\text{peak}}$ (mL·kg$^{-1}$·min$^{-1}$) was calculated from established age and sex norms (Jones and Campbell 1982) for comparison of cardiopulmonary fitness across age and sex.

2.3.5 Exercise Prescription and Progression

Participants in both stroke and cardiac streams of the CR program attended once-weekly, 90-minute supervised sessions of aerobic and resistance training (AT+RT) with the balance of
exercise conducted offsite (4 additional AT and 1-2 additional RT sessions). The staff-to-patient ratio of the TRI-REPS program was higher than the traditional cardiac program (1:5 vs. 1:12 respectively). All exercise sessions were tracked via individual exercise diary. The mode of AT and type of RT exercises were prescribed depending on individual ability. The AT goal for both cohorts was to progress patients to 20-60 minutes of exercise (Gordon et al. 2004), 5 times-wk<sup>-1</sup> (Hamm and Kavanagh 2000). For patients with CAD, the aerobic training prescription was set at an intensity equivalent to 40%-80% of VO<sub>2peak</sub> (ACSM 2009) and/or the level at which the VAT occurred (Gordon and Scott 1995). Patients were given a target distance and duration to complete. Prescriptions were progressed every 2 weeks to a maximum of 6.4 km and then to a maximum intensity of 80% of VO<sub>2peak</sub> as tolerated. Initial exercise intensity for individuals following stroke considered a combination of the following: the heart rate achieved at the VAT; 40-70% of heart rate reserve; and the heart rate that occurred at 40-70% of VO<sub>2peak</sub> (Gordon et al. 2004). Exercise diary information, heart rates measured at the center, as well as communication with the patient assisted the case manager in deciding when to increase the intensity and/or duration of the AT exercise (Hamm and Kavanagh 2000). For both cohorts the intensity of the initial prescription and subsequent exercise was adjusted to achieve a rating of perceived exertion (RPE) of 11-16 (“light” to “hard”) (ACSM 2009) on the Borg 6-20 scale (Borg 1982).

The CAD cohort was prescribed an RT routine of 10 exercises targeting the lower body (3 exercises), upper body (5 exercises), and the trunk (2 exercises) as described elsewhere (Marzolini et al. 2010). For the stroke cohort, the choice and number of RT exercises were based on the patients’ goals, gait pattern, grip strength, joint range-of-motion, presence or degree of hypertonicity, and balance. The exercises were task specific, incorporating muscle actions that are performed during daily activities, emphasizing re-training of balance, coordination, body weight support, weight shifting, and incorporating multi-joint movements. Resistance was provided by hand-held dumbbells, exercise bands (wrist/ankle attachments), or patients’ body weight. A weight load equivalent to 50-60% of 1 repetition maximum (1RM) was prescribed on the non-affected limb. On the hemiparetic limb, ≥50% of 1RM and/or a resistance rated as 13-14 on the RPE scale on the last repetition of the set was prescribed (Marzolini et al. 2008). Patients in both cohorts, gradually progressed from 1-2 sets and then from 10-15 repetitions and then
increased resistance by 1.6-5 kg or increased the exercise band level and then reduced repetitions to 10 and repeated this process.

### 2.3.6 Criteria to Determine Feasibility of CPET for Exercise Prescription

To determine if the CPET provided adequate information to develop an effective exercise prescription, at least 1 of the 3 following intensity levels had to be attained on the CPET: 1) Maximal oxygen uptake, i.e. $\dot{V}O_{2\text{max}}$; 2) VAT; 3) a CRA that would prohibit an exercise prescription beyond the intensity where it occurred (see below). $\dot{V}O_{2\text{max}}$ and VAT were determined by 2 independent assessors experienced in threshold analysis blinded to either the objectives of the study or patient diagnoses. Disagreements were resolved by consensus.

The first criterion, $\dot{V}O_{2\text{max}}$, was determined based on attainment of ≥1 of the following: 1) an oxygen uptake plateau at the end of the CPET defined as an increase of <2.1 mL·kg$^{-1}$·min$^{-1}$ of oxygen (Howley, Bassett and Welch 1995) for ≥60 seconds despite an increase in work rate, concomitant with a respiratory exchange ratio (RER) of ≥1.15 (Issekutz, Birkhead and Rodahl 1962) or 2) an RER of ≥1.15 concomitant with a peak heart rate within 10 beats/minute of age-predicted maximum defined by the formula $220 - \text{age (years)}$ (Fox, Naughton and Haskell 1971) or using the validated equation ($HR_{\text{max}}=164-0.7\times\text{age}$) (Brawner et al. 2004) for patients taking β-blockade medication.

The second criterion, the VAT, was determined by a combination of the V-slope method and the ventilatory equivalents methods (Beaver, Wasserman and Whipp 1986; ATS 2003). The V-slope method was defined as the point of departure from linearity of carbon dioxide output plotted against oxygen uptake. The ventilatory equivalent method was defined as the level corresponding to the rise in ventilatory equivalent of oxygen that occurs without a concurrent rise in the ventilatory equivalent of carbon dioxide. The VAT is considered a valid measure demonstrating high reproducibility and low interobserver variability when established standards are followed (Sullivan and Cobb 1990; Meyer et al. 1996).
Finally, CRA criteria were defined as abnormalities that would prohibit exercise beyond the intensity where it occurred, indicating increased risk of an acute cardiac event, or elevated mortality risk. These included the appearance of horizontal or downsloping ST-segment depression of ≥0.10 mV (1 mm) 80 ms past the J point on the ECG (ACSM 2009), angina pectoris or chest pain developed with exertion, or complex or high grade ventricular arrhythmia (frequent multiform ventricular premature beats (VPBs; ≥3 in 10 beats), runs of ventricular tachycardia (≥3 consecutive VPBs) (ACSM 2009), or exercise induced bundle branch block).

Patients in both cohorts who had a CRA on the CPET underwent an ECG telemetry with blood pressure monitoring during the first exercise session (walking on a 200 meter track or stationary cycling) to establish a safe exercise intensity (i.e. below the level where the CRA occurred). Modifications to the exercise program to reduce risk of a CRA during exercise such as including a longer cardiovascular warm-up, taking nitroglycerin prior to exercise, exercising close to the time of peak effect of beta-blockade medication was prescribed.

2.3.7 Safety

Serious cardiovascular events were defined as death, myocardial infarction, sustained ventricular tachycardia lasting >30 seconds, syncope, cardiopulmonary arrest, or a clinical condition necessitating cardiopulmonary resuscitation

2.4 Results

The proportion of CPETs that provided information sufficient to prescribe exercise intensity, (i.e. \( \dot{V}O_{2\text{max}} \), VAT, or a CRA) for the stroke and CAD groups was 68.4% vs. 82.7% respectively (p=0.02) at baseline, and 84.7% vs. 83.8% respectively (p=0.9) at 6 months (Table 2.4, Figure 2.2).
Table 2.4 Data Informing the Exercise Prescription

<table>
<thead>
<tr>
<th>Data Informing Exercise Prescription</th>
<th>Baseline</th>
<th>6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAD N=98</td>
<td>Stroke N=98</td>
</tr>
<tr>
<td>≥1 of VAT, VO$_{2\text{max}}$, or CRA, n (%)</td>
<td>81(82.7)</td>
<td>67(68.4)*</td>
</tr>
<tr>
<td>VAT Discernible, n (%)</td>
<td>79(80.6)</td>
<td>66(67.3)*</td>
</tr>
<tr>
<td>VO$_{2\text{max}}$ Achieved, n (%)</td>
<td>36(36.7)</td>
<td>18(18.4)*</td>
</tr>
<tr>
<td>Clinically Relevant Abnormality, n (%)</td>
<td>12(12.2)</td>
<td>11(11.2)</td>
</tr>
<tr>
<td>≥1 mm (Horizontal/downsloping ST-Segment Depression)</td>
<td>2(2)</td>
<td>4(4)</td>
</tr>
<tr>
<td>Complex Ventricular Premature Beats</td>
<td>4(4.1)</td>
<td>6(6.1)</td>
</tr>
<tr>
<td>Frequent Multiform/ventricular Tachycardia, n</td>
<td>3/1</td>
<td>4/2</td>
</tr>
<tr>
<td>Chest Discomfort</td>
<td>2(2)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Chest Discomfort and Significant ST-segment depression</td>
<td>2(2)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Conduction abnormality or arrhythmia developing during exercise/recovery</td>
<td>2(2)</td>
<td>1(1)</td>
</tr>
</tbody>
</table>

*p=<0.05 and †p=<0.001 between CAD and Stroke

CAD=coronary artery disease, VAT=ventilatory anaerobic threshold, VO$_{2\text{max}}$=maximal oxygen uptake, CRA=clinically relevant abnormality
A CRA was observed in 11.2% and 12.2% of baseline CPETs conducted in patients with stroke and CAD respectively (p=0.8). This included 7/67 patients post-stroke (10.5%) with no documented history of CAD and 4/31 patients post-stroke (12.9%) with a documented history of CAD. A CRA occurred at 6 months in 10.6% (n=9) of stroke and 5.9% (n=4) of CAD (p=0.4) patients. Of individuals post-stroke with no previous history of CAD, 10.3% (6/58) had a CRA, and of those with a documented history of CAD 11.7% had a CRA (3/27) at 6 months.

Significantly fewer individuals post-stroke achieved VO$_2$ max at baseline than those with CAD (p=0.003) but at 6 months there was no significant difference (p=0.3). A greater proportion of persons with stroke versus CAD discontinued the CPET owing to non cardiovascular reasons at baseline (p=0.007) with no significant difference at 6 months between groups (p=0.9) (Table 2.5).

No serious cardiovascular events occurred during 183 CPETs conducted in persons following stroke and in 166 persons with CAD.
Table 2.5  Indications for Discontinuing the CPET

<table>
<thead>
<tr>
<th>Reasons for Discontinuing CPET</th>
<th>Baseline</th>
<th>6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAD N=98</td>
<td>Stroke N=98</td>
</tr>
<tr>
<td>Maximal oxygen uptake achieved, n (%)</td>
<td>36(36.7)</td>
<td>18(18.4)*</td>
</tr>
<tr>
<td>Cardiovascular indications, n (%)</td>
<td>15(15.3)</td>
<td>11(11.2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>8(8.2)</td>
<td>4(4.1)</td>
</tr>
<tr>
<td>Ventricular ectopy</td>
<td>1(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>2(2)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>2(2)</td>
<td>4(4.1)</td>
</tr>
<tr>
<td>ST-segment depression</td>
<td>1(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>ST-segment depression, chest pain, dyspnea</td>
<td>1(1)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Excessive increase in heart rate</td>
<td>0(0)</td>
<td>1(1)</td>
</tr>
<tr>
<td>Volitional fatigue, n (%)</td>
<td>41(41.8)</td>
<td>47(48)</td>
</tr>
<tr>
<td>Non cardiovascular reasons, n (%)</td>
<td>6(6.1)</td>
<td>18(18.4)*</td>
</tr>
<tr>
<td>Weakness in one leg</td>
<td>1(1)</td>
<td>7(7.1)</td>
</tr>
<tr>
<td>Leg pain</td>
<td>2(2)</td>
<td>2(2)</td>
</tr>
<tr>
<td>Discomfort due to equipment (seat/mouth piece)</td>
<td>3(3.1)</td>
<td>9(9.2)</td>
</tr>
<tr>
<td>Unknown, n (%)</td>
<td>0(0)</td>
<td>4(4.1)</td>
</tr>
</tbody>
</table>

CAD=coronary artery disease

Blood pressure=SBP >250 or ≥220 mmHg for diabetes or DBP >115 or ≥110 mmHg for diabetes

or failure to ↑ with an increase in work rate

*p=<0.05 between CAD and Stroke
Sex Differences

Women post-stroke were significantly less likely than men post-stroke (40% vs. 80.9%, respectively, p<0.001) and less likely than women with CAD (80%, p=0.002) to reach ≥ one of the critical levels used for determining exercise prescription (Figure 2.3). There was no significant sex difference in proportion of CRAs on the baseline CPET, or any further sex differences in proportion reaching $\dot{V}O_{2\text{max}}$, VAT, or a CRA on the 6 month CPET.

Baseline sex differences for patients following stroke are presented in Tables 2.1 and 2.2. Women entered CR at a higher stage of motor recovery of the leg and foot than men (both, p=0.006). Women reached a significantly lower baseline peak $\dot{V}O_{2\text{peak}}$ than men following stroke (52.1±20.8% vs. 67.9±26.3% of age- and sex- predicted normative values, p=0.005) and compared to women following CAD (72.6±16.7%, p<0.001). Women following stroke were significantly more likely to discontinue the baseline CPET owing to non-cardiovascular reasons than men (33% vs. 11.8%, p=0.01) including discomfort with the equipment (n=6), weakness in one leg (n=3), and leg pain (n=1). At 6 months, there were no significant differences in $\dot{V}O_{2\text{peak}}$ between women and men post-stroke (68.6±20.1% vs. 78.3±29.7% of age- and sex- predicted normative values, p=0.2) but differences in non-cardiovascular reasons for discontinuing the CPET remained (16.7% vs. 3.2% of women and men respectively, p=0.047).
2.5 Discussion

We have demonstrated herein that most patients following stroke achieve exercise intensities sufficient to inform the exercise prescription on both baseline and 6 month CPETs. In addition, no serious cardiovascular events occurred during graded exercise to peak effort. However, while most women following stroke were able to reach a suitable intensity for exercise prescription on the 6 month CPET, less than half of the baseline CPETs were of adequate intensity for exercise.
prescription determination. Indeed, women following stroke were more disadvantaged than both men post-stroke and women post CAD regarding baseline CPET utility. Age, type of stroke, time from stroke, stage of motor recovery, gait aid requirement, modality of testing, or frequency of CRAs did not explain the mitigated utility when compared to men post-stroke. Rather, reduced baseline CPET utility may, in part, be explained by the marked deconditioning in women following stroke at entry to CR. \( \dot{V}O_{2\text{peak}} \) was half of normative values and significantly lower compared to men following stroke and women with CAD. This may have accounted for women’s reduced ability to reach \( \dot{V}O_{2\text{max}} \) or VAT because more highly conditioned patients are more likely to attain maximal levels on a CPET (Sidney and Shephard 1977) and VAT is increasingly more likely to be determined in patients who attain a higher \( \dot{V}O_{2\text{peak}} \) (Meyer et al. 1996). While there is a paucity of data on sex differences in functional outcomes post-stroke, data from the Framingham Heart Study show that pre-stroke and post-stroke disability are significantly higher in women than men (Petrea et al. 2009). While motor recovery stage was higher for women than men in the present study, there may be functional differences that were not reflected by the CMSA score and not measured in this study, which may have also accounted for the poorer baseline performance in women. The finding that there was a preponderance of non-cardiovascular barriers that more frequently prevented women in reaching peak effort than men, including weakness and discomfort in one leg and intolerance of the exercise testing equipment, may be a reflection of greater disability.

Nevertheless, following 6 months of exercise training, utility of the CPET for women post-stroke was similar to men post-stroke and equal to women with CAD. In view of the superior CR completion rate of stroke compared to CAD patients, it is unlikely that this improvement can be explained by selective dropout. Rather, improved CPET utility from baseline may be due, in part, to gains in cardiovascular fitness on the 6 month test that placed women at a similar cardiovascular fitness level (age- and sex- normative values) to both men following stroke, and to women with CAD. Survivors of stroke have a physiological disadvantage compared to individuals following CAD as they exhibit muscle atrophy in the hemiparetic limb (Ryan et al. 2002) contributing to quadriceps muscle weakness (Harris et al. 2001). While sex differences in vascular and muscle morphology post-stroke have not been fully elucidated, a program of aerobic and resistance training may have mitigated these affects allowing women to reach a
higher intensity on the 6 month CPET. Indeed, greater leg strength has been shown to be associated with a higher \( \text{VO}_{2\text{peak}} \) in patients with CAD (Marzolini et al. 2008).

The improved cardiovascular fitness and ability of women to reach higher absolute intensity levels on the CPET after a program of resistance and aerobic training is of clinical significance given the disability and institutionalization rates in women post-stroke (Petrea et al. 2009). Combined with greater life expectancy and later onset of stroke in women compared to men (Petrea et al. 2009; Wyller 1999) indicate the growing importance of developing strategies to improve the feasibility of the initial CPET to inform exercise programming for women. In the interim, a CPET conducted mid-program (i.e. 3 months from start), may provide valuable information for prescribing exercise.

CPETs may involve risks for patients following stroke in view of the high incidence of CAD and associated risk factors. However, no serious cardiovascular events occurred during 183 graded exercise tests to peak effort. Nevertheless, more than 1 in 10 patients following stroke demonstrated a significant abnormality that would prohibit exercise beyond the intensity where it occurred on both baseline and follow-up CPETs. In addition, these abnormalities occurred equally in those with and without a comorbid history of CAD. Moreover, rate of clinically relevant abnormalities were equal to that of patients in the CAD cohort at both time points despite reaching a significantly lower CPET intensity (35% vs. 73% of age- and sex- predicted maximal heart rate respectively). Thus it is possible that the rate of abnormality is under represented in the stroke cohort in this study. Other studies employing coronary angiography, or thallium scintigraphy suggest a higher rate of abnormality in patients following stroke (Love et al. 1992; Amarenco et al. 2011).

### 2.6 Limitations

CR programs offer multiple CPET modality options as well as the experience and training to assess and manage patients with multiple comorbidities that may not exist in other facilities. Therefore, findings in this study may not be generalizable to all facilities or to all individuals
post-stroke referred to an exercise program, including those early in stroke recovery. While the VAT has been reported to be modality specific, almost half of stroke patients were prescribed a stationary cycle program either alone or in combination with a walking program. Finally, angiographic or perfusion imaging in stroke patients who exhibited abnormalities on the CPET is lacking.

2.7 Conclusions

The results of this study support the feasibility and utility of systematically conducting CPETs for those with chronic stroke both with and without CAD comorbidity prior to engaging in exercise. Prescription methods without this information may risk an exercise intensity that does not provide adequate cardiovascular stress to induce a training response or may precipitate a cardiovascular issue. At least 1 in 10 individuals post-stroke manifested a clinically relevant abnormality on stress testing that would require exercise modification; however there were no serious cardiovascular events during CPET or CR. With appropriate adaptation of exercise test protocols, most patients can achieve adequate exercise levels and cardiac safety issues can be identified. In view of the mitigated utility of the baseline CPET for prescribing exercise to women following stroke, strategies to identify and remove barriers that limit women in reaching these critical intensities require further investigation.

2.8 Acknowledgments

We acknowledge the contribution of Dr. D.J. Mertens, Rene Belliard, Walter Swardfager, and patients and staff at Toronto Rehab.
Chapter 3 CAN INDIVIDUALS PARTICIPATING IN CARDIAC REHABILITATION ACHIEVE RECOMMENDED EXERCISE TRAINING LEVELS FOLLOWING STROKE?


Susan Marzolini was Case Manager for the patients of this study and prescribed the aerobic and resistance training components as well as progression of exercise to each patient. Susan Marzolini also conceived and designed the research with Dr. Brooks, acquired the data, analysed and interpreted the data, performed statistical analysis and drafted the manuscript.

3.1 ABSTRACT

**Purpose:** Cardiac rehabilitation programs (CRP) have been recommended to provide exercise guidance post-stroke. However, it has not been established if minimal exercise training levels, sufficient for obtaining health benefits, can be attained in a CRP. Therefore, we assessed the ability of stroke patients to achieve recommended exercise levels during a single standard CR session following completion of a CRP.

**Methods:** Sixteen patients (10m, 6f) with mild/moderate motor impairments who had completed a CRP participated in the study. Resting metabolic rate (RMR) and oxygen uptake during 30 minutes each of aerobic and resistance training were assessed by ambulatory oxygen monitor. Obtained values were compared to recommended minimal levels i.e., ≥20 minutes of exercise at ≥40% of peak oxygen uptake (\(\dot{V}O_2\text{peak}\)), ≥30 minutes of exercise at ≥3 METs (multiples of RMR), and an energy expenditure of approximately 200 kcal-session\(^{-1}\).

**Results:** Mean time sustaining ≥40% of \(\dot{V}O_2\text{peak}\) was 47.6±9 minutes; exceeding the minimal target of 20 minutes (p<0.001). Time sustaining ≥3 METs was 30.8±12.2 minutes, matching the target of 30 minutes (p=0.8). Total energy expenditure (252±49.9 kcal) was significantly greater than the target value of 200 kcal (p=0.001).
**Conclusion:** Chronic stroke patients with mild/moderate motor impairments are able to meet or exceed minimal recommended exercise target levels for intensity, duration and energy expenditure during a typical exercise session consisting of 30 minutes of AT combined with 30 minutes of RT after completing a CRP. These data contribute to the evidence promoting the efficacy and feasibility of a CRP for people following stroke.

### 3.2 INTRODUCTION

Significant cardiovascular deconditioning and muscle weakness are well established sequelae of stroke (Michael and Macko 2007) and contribute to the impairment that has made stroke a leading cause of severe chronic disability among adults (Adamson, Beswick and Ebrahim 2004). Post-stroke survival is significantly affected by concomitant coronary artery disease (CAD), the incidence of which has been reported to occur in up to 75% of stroke survivors (Roth 1993). It is becoming increasingly evident that reversing deconditioning through regular physical activity may play a role in the secondary prevention of stroke and CAD (Gordon et al. 2004; Kavanagh et al. 2002).

Despite the growing recognition of the importance of exercise training after stroke, exercise-based programs are not widely available for chronic stroke patients (Tang et al. 2009). Cardiac rehabilitation (CR) programs can potentially provide long-term programming to supplement conventional stroke rehabilitation (Furie et al. 2011). However, the ability of stroke patients to participate in CR and to achieve recommended minimal levels of exercise and energy expenditure have not been investigated. Of concern, is that physical activity levels may be limited by a constellation of neurological impairments as well as comorbidities. Accordingly, the purpose of this study was to investigate the efficacy of CR in patients who were at least 3 months post-stroke. We hypothesized that the acute exercise oxygen uptake measured during a standard 60 minute AT and RT session would reach the minimal intensity recommendation of 40% of VO\textsubscript{2peak} for a duration of at least 20 minutes.
3.3 Methods

This was a single group study, designed to measure the physiological responses to 60 minutes of AT and RT after participation in a 6 month CR program adapted for stroke patients as well as overall pre- and post-program performance. The study was approved by the institutional Research Ethics Boards and informed written consent was obtained from each subject.

In that a single metric of exercise performance does not provide a robust assessment of an exercise session, we chose to consider 3 metrics in this study. Based on the dose-response relationship between exercise and health related outcomes, the recommended energy expenditure (EE) in kcal, associated with exercise to elicit benefits in health for most adults is approximately 1,000 kcal-wk$^{-1}$ (ACSM 2009; Garber et al. 2011). This translates to 200 kcal/exercise session, 5 times-wk$^{-1}$. Therefore, EE during a standard CR exercise session was included as a metric in the current study.

Second, exercise intensity is believed to be the primary factor responsible for changing peak oxygen uptake ($\dot{V}O_{2\text{peak}}$) (Gormley et al. 2008; Lam et al. 2010; Swain 2005; Swain and Franklin 2002), with greater $\dot{V}O_{2\text{peak}}$ associated with lower mortality rates in patients with CAD as well as in the general population (Blair et al. 1995; Kavanagh et al. 2002). Moreover, some studies report that moderate to high intensity physical activity in itself may be a greater determinant of primary stroke prevention than total EE (Willey et al. 2009; Lee, Folsom and Blair 2003; Lee and Paffenbarger 1998). Thus, as a measure of exercise intensity, oxygen uptake was measured during a single CR exercise session, reported relative to the $\dot{V}O_{2\text{peak}}$ obtained on a 6 month cardiopulmonary exercise test (CPET) and then compared to the minimal recommendation of 20 minutes at 40% of $\dot{V}O_{2\text{peak}}$.

Unfortunately, in stroke patients, any measure of intensity that is relative to achievement of a percentage of $\dot{V}O_{2\text{peak}}$ may vary depending upon stroke-related factors unrelated to cardiovascular endpoints (e.g., neuromuscular disability, cognitive deficits) and affect CPET termination. Therefore, the third metric of exercise intensity was the attainment of an adequate
metabolic equivalent (MET) level ie, multiples of resting metabolic rate (RMR); a measure unrelated to CPET performance. Current activity guidelines advocate maintaining an exercise intensity of ≥3METs for 30-60 minutes, 5 d-wk⁻¹ for healthy adults (Haskell et al. 2007).

3.3.1 Participants

Persons living in the community who had experienced a stroke at least 3 months previously were referred to Toronto Rehabilitation Institute’s Risk Factor Modification and Exercise Program following Stroke (TRI-REPS) from outpatient stroke rehabilitation programs and primary care physicians. Consecutively enrolled patients were invited to participate in the study. Patients were eligible for the study if they had a mild/moderate leg impairment score of 3 (marked spasticity and weakness) to 6 (near normal coordination of patterns of movement and no spasticity) on the 7-point Chedoke-McMaster Stroke Assessment scale (CMSA), (Gowland et al. 1993) ability to ambulate ≥10 meters independently with/without gait aids, and no contraindications to maximal exercise testing (ACSM 2009). Higher functioning patients with no stroke-related motor impairments were included in the regular CR stream and not included in the study. Medical information and patient comorbidities were collected upon referral.

3.3.2 Adapted CR Program

The TRI-REPS program for stroke patients was similar in design to the traditional CR program (Hamm and Kavanagh 2000). Patients attended a 90 minute exercise class 1 time-wk⁻¹ for 6 months. The case manager prescribed an individualized AT program in the first weekly session, followed by an RT program in the following session. Patients were then assigned to 1 of 4 exercise groups (maximum of 5 patients in each group), each supervised by an exercise leader. Patients were advised to complete 4 additional AT and 1-2 RT sessions at home, and these were tracked via exercise diary and recorded.
The mode of AT was prescribed depending on patient ability and access to equipment when away from the center. Treadmill or outdoor walking was considered primarily for those who were not only capable of independent ambulation, but who could also sustain high enough speeds and durations to achieve aerobic benefit. Cycle ergometry was prescribed when stroke-related deficits precluded walking since the feet could be affixed to the pedals (Tang et al. 2006). The AT prescription was based on data from the CPET conducted at program entry. The goal was to progress patients to 20-60 minutes of exercise, 5 times-wk⁻¹ at an intensity considering a combination of the following: 40-70% of heart rate reserve or $\text{VO}_{2\text{peak}}$, the heart rate achieved at the ventilatory anaerobic threshold (VAT) (Gordon and Scott 1995) determined by a combination of the V-slope method and the ventilatory equivalents methods (Beaver, Wasserman and Whipp 1986; ATS 2003). The initial exercise prescription was adjusted to achieve an exercise intensity rated as 11-16 (“light” to “hard”) on the Borg 6-20 perceived exertion (RPE) scale (Borg 1982). Exercise diary information, heart rates measured at the center, and communications with the patient assisted the case manager in adjusting the AT intensity and/or duration. Interval training, characterized by short periods of increased exercise intensity alternating with longer periods of lower intensity exercise, was prescribed to patients when a faster speed did not preclude safety.

The choice and number of RT exercises were based on patient goals, gait pattern, grip strength, joint range-of-motion, presence or degree of hypertonicity, and balance. The exercises were task specific, incorporating muscle actions that are performed during daily activities, emphasizing retraining of balance, coordination, body weight support, weight shifting, and incorporating multi-joint movements. Resistance was provided by hand-held dumbbells, exercise bands (wrist/ankle attachments), or patient body weight. A weight load equivalent to 50-60% of 1 repetition maximum (1RM) was prescribed on the nonaffected limb. On the hemiparetic limb $\geq 50\%$ of 1RM and/or a resistance rated as 13-14 RPE on the last repetition of the set was prescribed (Marzolini et al. 2008). When patients were ready to perform RT at home (typically after 2-3 supervised sessions), a booklet was provided, including instructions for lifting weights safely, progression of exercises, and pictures and written descriptions of each exercise. Patients gradually progressed from 10 to 15 repetitions, increasing resistance by 1.6-5 kg or increasing the exercise band level as appropriate and reducing repetitions to 10 and repeating this process.
Sets could also be increased from 1 to 2. Progression was guided by patient performance during the exercise class and exercise diary information.

### 3.3.3 Measures

A symptom-limited CPET on a recumbent cycle ergometer with specialized pedals to secure feet (Ergoline Select 1000, Germany) or upright cycle (Ergoselect 200P, Germany) was performed by 9 and 7 patients, respectively, at baseline and after 6 months of training. The type of ergometer was chosen based on balance and control of leg/foot position in the pedals. Work load was increased by either 8.3 or 16.7 Watts every minute. Breath-by-breath gas samples were collected (SensorMedics Vmax Encore, San Diego CA). At baseline, patients also performed a 6 minute walk test (ATS 2002). Results were reported according to percentage of predicted norms (Enright and Sherrill 1998). Maximal strength was determined at baseline and after 6 months of training using the 1RM test as described elsewhere (Marzolini et al. 2008). Finally, cognition was measured at baseline using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al. 2005).

### 3.3.4 Oxygen Uptake During a Single Exercise Session

Patients underwent a physiologic assessment during a 60 minute exercise session upon completion of 6 months of CR. Evaluation of RMR was followed by oxygen uptake assessment during 30 minutes of AT, followed by 30 minutes of RT using the CORTEX Biophysik MetaMax®3X portable gas analyzer, Leipzig Germany (Schulz, Helle and Heck 1997). Prior to each assessment, volume and gas calibrations were completed according to the manufacturer instructions. Ventilatory data were averaged over each minute for calculation of RMR and EE. Ventilatory values were also recorded every 10 seconds for calculation of the amount of time exercising at intensities relative to $\text{VO}_2^{\text{peak}}$ and METS. Data were included in the analyses when $\geq 3$ consecutive 10 second intervals reached target values.
Patients were advised to fast and avoid caffeine 12 hours prior and not to undertake any planned exercise 24 hours prior to the assessment. RMR was measured over a 30 minute period with subjects awake and in a semi-reclined position. Following RMR measurement, patients were provided with a 200 kcal breakfast bar. Fifteen minutes later, patients performed 30 minutes of AT followed by a 10 minute recovery period and then a 30 minute bout of RT.

### 3.3.5 Exercise Training Regimen

**Aerobic Training.** Patients were instructed to perform the aerobic training prescription most recently prescribed and regularly carried out at home as reflected in the exercise diary. No prompting was provided by the staff monitoring the exercise except to instruct on initiation and cessation of exercise. Gait speed was recorded after completion of each lap of a 200 meter track.

**Resistance Training.** Patients were instructed to perform RT prescription most recently prescribed, including type of exercise, load lifted, and number of repetitions as recorded on recent exercise diaries. In order to standardize the exercise between patients, a 60 second rest between sets was allowed, and initiation of each exercise was prompted by the testing staff.

### 3.3.6 Analyses

The main items of interest were the total EE and intensity of acute exercise measured over the 60 minute exercise session. The ambulatory device software allowed mean oxygen uptake to be collected in intervals of at least 10 seconds in duration in both mL·kg\(^{-1}\)·min\(^{-1}\) for calculation of relative intensity, and liters of oxygen for calculation of EE. Thus, the amount of time in which oxygen uptake was sustained at an exercise intensity of ≥40% of \(\dot{V}O_{2\text{peak}}\) (mL·kg\(^{-1}\)·min\(^{-1}\)) and ≥3METs for intervals of at least 30 consecutive seconds (≥3 consecutive 10 second intervals) was contrasted to the minimal recommendation of 20 minutes and 30 minutes duration respectively, using an independent one-sample \(t\) test statistic. The mean total EE achieved was
compared to the recommendation of 200 kcal·session⁻¹, 5 times·wk⁻¹ using an independent one-sample \( t \) test statistic. EE data (liters of oxygen) was averaged and recorded over each minute of exercise. EE was estimated using a constant value of 5.05 kcal·L⁻¹ of oxygen. (Wilmore et al. 1978) The energy expended over 60 minutes was then calculated. Results were reported as mean ± SD. Probability values <.05 were considered significant.

### 3.4 Results

Of 21 consecutively enrolled patients in the CR program, 16 (6 female) agreed to participate in the study. Mean age was 60.8±13.7 years and 20.2±38.5 months had elapsed since their stroke (Table 3.1). Reasons for not participating were perceived discomfort of the apparatus (mask) due to sinus problems - 1, too busy - 2, discontinuation of CR owing to re-occurrence of cancer - 1, and transportation difficulties - 1. All patients had mild/moderate motor impairments (mean CSMA leg score of 4.9±0.9, range of 3-6) and most patients (60%) scored <25 on the MoCA indicating mild cognitive impairment (Pendlebury et al. 2012; Pendlebury et al. 2010). Of all patients, 25% had a concomitant diagnosis of diabetes and 19% had CAD. Most patients (81%) used a gait aide for ambulation.

Baseline \( \dot{V}O_2\text{peak} \) (mL·kg⁻¹·min⁻¹) of 16.3±5.7 increased to 18.5±4.5 \((P<.001)\) after 6 months of training. Based on exercise diaries submitted, patients completed a mean of 4.6±1.2 AT sessions/week and 1.7±0.4 RT sessions per week over the 6 month program. Patients attended 89.6±7.3 % of weekly supervised sessions.
Table 3.1 Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, n (m/f)</td>
<td>16 (10/6)</td>
</tr>
<tr>
<td>Age, years</td>
<td>60.8 ± 13.7 (41-88)</td>
</tr>
<tr>
<td>Time post-stroke, months</td>
<td>20.2 ± 38.5 (3-160)</td>
</tr>
<tr>
<td>Ischemic stroke type n (%)</td>
<td>7 (44)</td>
</tr>
<tr>
<td>LAD, SAD, unknown etiology n (%)</td>
<td>4(57)/2(28.6)/1(14.3)</td>
</tr>
<tr>
<td>Hemorrhagic stroke type, n (%)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Right/Left hemisphere affected, n (%)</td>
<td>7 (44)/9 (56)</td>
</tr>
<tr>
<td>Cardiovascular history, n (%)</td>
<td></td>
</tr>
<tr>
<td>&gt;1 stroke</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Gait aids, None/Cane/Rollator, n (%)</td>
<td>3 (18.8)/10 (62.5)/3 (18.8)</td>
</tr>
<tr>
<td>Chedoke-McMaster Stroke Assessment scores</td>
<td></td>
</tr>
<tr>
<td>Arm/Hand</td>
<td>4.4 ± 1.8 (2-7)/3.9 ± 2.2 (1-7)</td>
</tr>
<tr>
<td>Leg/Foot</td>
<td>4.9 ± 0.9 (3-6)/3.9 ± 1.8 (1-7)</td>
</tr>
<tr>
<td>Peak Oxygen Uptake (ml∙kg∙min⁻¹)</td>
<td>16.3 ± 5.7</td>
</tr>
<tr>
<td>Body Mass Index (kg/m2)</td>
<td>25.8 ± 4</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>94.3 ± 11.2</td>
</tr>
<tr>
<td>Six Minute Walk Distance, metres</td>
<td>272 ± 114.6</td>
</tr>
<tr>
<td>% of age, height, weight, sex predicted norm</td>
<td>50.7 ± 21.7</td>
</tr>
<tr>
<td>Cognition (MoCA score) n=15</td>
<td>22.7 ± 4.2 (16-30)</td>
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<tr>
<td>Mild Cognitive Impairment (score&lt;25),n %</td>
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</tr>
<tr>
<td>Medications, n(%)</td>
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</tr>
<tr>
<td>ß-blockers</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Ca²⁺-channel antagonists</td>
<td>5 (31.3)</td>
</tr>
<tr>
<td>Other Antihypertensives</td>
<td>13 (81.3)</td>
</tr>
<tr>
<td>Lipid lowering agents</td>
<td>9 (56.3)</td>
</tr>
</tbody>
</table>

LAD=Large Artery Disease

SAD=Small Artery Disease

MoCA=Montreal Cognitive Assessment

### 3.4.1 Exercise Characteristics during a Single Exercise Session

**Aerobic Exercise.** Walking was the predominant mode of AT (n=11, 69%), followed by stationary cycling (n=2, 13%), a combination of walking and cycling (n=2, 13%), and walking and elliptical exercise (n=1, 6%). Among those who only walked, the mean distance completed in 30 minutes was 1,706±723 meters (range 800-3100m) at a velocity of 0.88±0.4 m·sec⁻¹. Interval training was performed by 56% of the patients (5 walking, 2 cycling, and 2 walk/cycling combination) and included periods of high intensity exercise (mean of 43±31 seconds) and periods of moderate intensity exercise 5-10 minutes in duration. All 9 patients completed ≥3 fast intervals. Mean RPE immediate post-AT for all patients was 13.5±1.3.

**Resistance Training.** Patients completed a mean of 12±1.7 RT exercises (range 9-14). Of these exercises, 57.4% were lower body exercises (n=7.5±1.8), 31.5% were upper body (n=4±1.5), and 11% were core muscle exercises (n=1.3±0.5). In addition, 25.7% included hand-held dumbbells, 22% included elastic bands, and 52.3% included the patient-own body mass as resistance. While each program was individualized, the forward lunge, standing squat, and bicep curl exercises were
common to all patients. The mean intensity of the bicep curl was 53.5% of 1RM for the non-paretic arm and 78.2% of 1RM for the paretic arm (n=12 patients); 4 patients were unable to complete 1RM testing on the paretic arm. The mean RPE of the last repetition at immediate completion of the RT program was 13.3±2.

3.4.2 Mean Intensity of Exercise During a Single CR Session

The mean \( \dot{VO}_2 \) elicited during a single 60 minute exercise session was 10.5±1.7 mL·kg\(^{-1}\)·min\(^{-1}\) (range 6.5-12.6). This represented 59±13.5% of \( \dot{VO}_2\text{peak} \) and exceeded the recommended target level of 40% of \( \dot{VO}_2\text{peak} \). Mean \( \dot{VO}_2 \) for the 30 minute periods was 12.6±2.3 mL·kg\(^{-1}\)·min\(^{-1}\) (71%±20.2 of \( \dot{VO}_2\text{peak} \)) and 8.5±1.7 mL·kg\(^{-1}\)·min\(^{-1}\) (47%±9 % of \( \dot{VO}_2\text{peak} \)) for AT and RT, respectively (Figure 3.1).
3.4.3 Amount of Time Meeting Target Exercise Intensity

The mean exercise time sustaining ≥40% of $\dot{V}O_{2\text{peak}}$ was 47.8±9 minutes (range 27-59 minutes) during the 60 minute exercise session. This was greater than the recommended minimal target level of 20 minutes ($P<.001$) and all patients met this target (Figure 3.2). Of the total time sustaining ≥40% of $\dot{V}O_{2\text{peak}}$, AT contributed 60.7% and RT 38.9% of the time at this intensity (difference, $P<.001$). Mean total time sustaining ≥50%, ≥60%, and ≥70% of $\dot{V}O_{2\text{peak}}$ compared to 20 minutes was 38.1±3.3 ($P<.001$), 27.3±3.6 ($P=.06$), and 17.5±12 ($P=0.4$), respectively. Most patients (56.3%) were able to reach an intensity of ≥70% of $\dot{V}O_{2\text{peak}}$ for ≥20 minutes. Also, the mean total time at or above the VAT was 11.4±14.2 minutes ($P=.03$ compared to 20 minutes). Mean time exercising at ≥3METs was 30.8±12.2 minutes (range 3.3-54 minutes), which matched the guideline target level of 30 minutes ($P=.8$) (Figure 3.2). AT and RT time sustained at ≥3METs was 24.5 vs. 6.3 minutes, respectively (difference, $P<.001$); 7 patients (44%) did not reach the target duration of 30 minutes at ≥3METs.
Figure 3.2. Exercise Time at Target Intensities (≥3 METS and ≥40% of VO₂peak)

AT=aerobic training, RT=resistance training
(a) indicates p<0.001 difference in time at ≥40% of VO₂peak between AT+RT exercise and target value.

3.4.4 Energy Expenditure During a Single Exercise Session

The mean total EE for a single session (252±49.9 kcal, range 175-346) was significantly greater than the target value of 200 kcal (P=.001). Only 2 patients (12.5%) were unable to reach this target having a deficit of 25 and 16 kcal. AT and RT contributed a mean of 150.2 and 101.8 kcal, respectively, to the total EE (difference, P<.001), representing 59.6% and 40.4% of the total EE, respectively.
3.5 Discussion

We have shown that persons living with a stroke with mild to moderate motor impairments are able to successfully participate in an adapted CR program and progress to an activity level associated with positive modification of cardiovascular risk. Results demonstrated that participants were able to meet or exceed minimal target levels for intensity, duration, and EE recommendations. Indeed, most patients were able to maintain an exercise intensity of at least 70% of the 6 month VO\textsubscript{2peak} (upper end of the recommended intensity zone) for a minimum of 20 minutes. Together with compliance and improved cardiovascular fitness findings, these data contribute to the evidence promoting the efficacy and feasibility of an adapted CR program for people following stroke (Tang et al. 2010; Jurkiewicz, Marzolini and Oh 2011).

While this study measured oxygen uptake during combined AT (30 minutes) and RT (30 minutes), carrying out RT on consecutive days is not recommended. Thus, on days when AT is carried out alone, AT duration should be extended to approximately 40 minutes to achieve weekly recommended EE targets. Furthermore, while AT activity contributed more to achievement of recommended exercise levels than RT, the contribution of RT was noteworthy. Typically, RT is not prescribed with the goal of improving cardiovascular fitness but nonetheless has been shown to contribute to an augmented cardiovascular benefit, when combined with AT compared to AT alone in cardiac patients (Marzolini et al. 2008). In the present study the mean VO\textsubscript{2} over 30 minutes of RT (46.9% of VO\textsubscript{2peak}) was within the target training zone, accounting for 40% of total EE and 19 minutes of time spent at ≥40% of VO\textsubscript{2peak}. The contribution of RT may be due to the characteristics of the exercises prescribed ie, mostly lower body, weight bearing exercises, engaging large muscle groups requiring balance, and coordination. This is an important finding for the prescription of exercise for patients with gait deficits that prohibit reaching a walking velocity sufficient to achieve recommended intensity levels for improving cardiovascular fitness. RT exercises can be carried out in the home, the equipment is relatively inexpensive, and exercises can be modified to accommodate the functional level of the patient.
A potential limitation of using time at ≥40% of \( \dot{V}O_{2\text{peak}} \) as a metric of beneficial exercise post-stroke is the dependence on patient CPET performance. However, in this study, patients achieved near physiological maximal levels as demonstrated by a mean peak respiratory exchange ratio of 1.12 supporting the relevance of this guideline for exercise prescription and evaluation in this cohort. In contrast, while the use of METs for measuring intensity is not relative to CPET performance, the inherent limitations are that moderate activity of 3 METS may be too vigorous for an unfit older person or not vigorous enough for a fit younger person (Howley 2001). Thus, it was not surprising that not all patients were able to sustain an intensity of ≥3METs for 30 minutes.

The sample of 16 subjects, young age, and exclusion of patients who were not able to walk ≥10 meters with/without gait aid, limits the generalizability of this study. However, while heterogeneity among stroke patients is well reported, the physical profile is consistent with other studies, and the high prevalence of mild cognitive deficits (60%) is consistent with that previously reported in the stroke population (64%) (Macko et al. 2005; Ya-Ping et al. 2006).

### 3.6 Conclusions

Reaching target exercise levels are important following stroke as deficits in the amount of planned, intentional physical activity are not likely to be compensated for by spontaneous lifestyle physical activity, given the well documented post-stroke patterns of inactivity at home and in the community (Michael and Macko 2007). However, given the dose-response association between volume of exercise and health related outcomes, patients unable to reach recommended training levels may still achieve benefit from less exercise (Wen et al. 2011). Results suggest that chronic stroke patients with mild/moderate motor impairments attending outpatient CR are able to achieve minimal recommended exercise levels during a typical exercise session consisting of 30 minutes of AT combined with 30 minutes of RT. Further investigation of increased intensity interval training and other exercise options, including RT, to augment exercise programming, is warranted.
Chapter 4 PHYSIOLOGICAL OUTCOMES IN INDIVIDUALS FOLLOWING STROKE ATTENDING AN ADAPTED CARDIAC REHABILITATION EXERCISE PROGRAM: DOES TIME FROM STROKE MAKE A DIFFERENCE?

Susan Marzolini was Case Manager for the patients of this study and prescribed the aerobic and resistance training components as well as progression of exercise to each patient. Susan Marzolini also conceived and designed the research with Dr. Brooks, acquired the data, analysed and interpreted the data, performed statistical analysis and drafted the manuscript.

4.1 ABSTRACT

Background: Individuals referred to cardiac rehabilitation programs (CRP) following stroke have demonstrated post-program improvements in cardiovascular fitness. However, other stroke recovery outcomes and the effects of time-from-stroke have not been investigated.

Purpose: To 1) evaluate physiological effects of a 24-week CRP of resistance and aerobic exercise in 120 participants with stroke, and 2) examine group differences between participants ≤1 year vs. >1 year post-stroke.

Methods: Primary outcomes included 6-Minute Walk distance (6MWD), timed repeated sit-to-stand performance, cardiovascular fitness determined by peak oxygen uptake in mL·kg·min⁻¹, and affected-side isometric knee extension strength (IKES). Secondary measures included fast-paced gait characteristics and speed, balance, range of motion, affected-side elbow flexion and grip strength, anaerobic threshold, and perceptions of participation/social reintegration.

Results: After adjusting for multiple comparisons, participants demonstrated improvement in 6MWD (283.2±126.6-320.7±141.8 meters, p<.001), timed sit-to-stand performance (16.3±9.5-13.3±7.1 seconds, p<.001), affected IKES (25.9±10.1-30.2±11 kg of force as a % of body mass, p<.001), and cardiovascular fitness (15.2±4.5-17.2±4.9 mL·kg⁻¹·min⁻¹, p<.001). While those who began the program ≤1 year and >1 year post-stroke showed improvements in all outcomes (p<.005), participants who started ≤1 year post-stroke had greater improvements in 6MWD than
those >1 year post-stroke (31.2±10.6 meter difference, p=.004). Participants also demonstrated post-CRP improvements in secondary functional/psychosocial outcomes: fast walking speed and cadence, anaerobic threshold, balance, range of motion, perception of participation, and affected-side grip and isometric elbow flexion strength (all p<0.001). However, there were greater improvements in fast walking speed and non-affected-side step length for those referred ≤1 year compared to >1 year post-stroke (p<0.05).

**Conclusion:** A CRP yielded improvements over multiple domains of recovery. While those referred ≤1 year and >1 year post-stroke derive benefits from CRP, those who start earlier have greater improvements in ambulatory performance.
4.2 Introduction

Evidence is accumulating that cardiac rehabilitation (CR) programs can provide exercise programming for individuals following traditional stroke rehabilitation (TSR) (Marzolini et al. 'Can Individuals Participating in Cardiac Rehabilitation Achieve Recommended Exercise Training Levels Following Stroke?' 2012; Marzolini et al. 'The Feasibility of Cardiopulmonary Exercise Testing for Prescribing Exercise to People after Stroke' 2012; Tang et al. 2010; Lennon et al. 2008). Given the elevated risk for recurrent stroke and potential for exercise to mediate many of the modifiable stroke risk factors, the exercise training components as well as risk factor interventions and assessments offered by interprofessional health care CR teams are suited to long-term health behavior change appropriate for individuals following stroke. These include aerobic and resistance training, as well as nutrition and psychosocial counseling. In view of the high incidence of coexisting health issues such as diabetes and coronary artery disease, these components are important but may not be available in a TSR facility.

While research evaluating the efficacy of adapted CR programs after stroke have focused on one key exercise-related outcome, cardiovascular fitness ($\text{VO}_{2\text{peak}}$), (Tang et al. 2010; Lennon et al. 2008) other dimensions of stroke recovery need to be considered. This is of importance as stroke patients are left with limitations (Jorgensen et al. 1995) that affect complex coordinated functioning such as mobility, ambulation, and sit-to-stand performance, as well as underlying muscular weakness that can contribute to functional limitations (Canning, Ada and O'Dwyer 2000; Pound, Gompertz and Ebrahim 1998; Flansbjer, Downham and Lexell 2006). Given that these issues may affect health related quality-of-life and disability dimensions, such as perceived participation, social reintegration and independence (Flansbjer, Downham and Lexell 2006) it is not surprising that the most frequently stated goal by individuals following stroke is to improve ambulation endurance and independence (Bohannon, Andrews and Smith 1988). While it is not uncommon for patients participating in a TSR program to reach a recovery plateau in one or more of these areas (Page, Gater and Bach-y-Rita 2004), there may be further potential for improvement if individuals are referred to a CR program. The recovery plateau in TSR may
merely represent a normal pattern of adaptation to routine therapy lacking progression and modulation in intensity and duration parameters. It has been posited that further improvement may be possible following TSR with a stimulus that is either greater or different than that offered in TSR programs (Page, Gater and Bach-y-Rita 2004). Adapted CR programs that include long-term individualized resistance and aerobic training with gradual progression of intensity and duration parameters may result in improvements in these areas but this has not been previously investigated. Thus, ambulatory and sit-to-stand performance, paretic-side leg strength, and \( \dot{V}O_2^{peak} \), were the primary outcome measures for investigation.

Another issue that merits examination is the efficacy of adapted CR treatments in relation to time elapsed post-stroke. Most studies report diminishing gains in functional recovery over time, with little or no change reported 3 to 6 months post index event (Wade and Hewer 1987; Jorgensen et al. 1995; Kelly-Hayes et al. 1989; Parker, Wade and Langton-Hewer 1986). While interventions in the earlier recovery period (<3 months) offer the greatest potential for change, participants of adapted CR programs are typically referred at least 3 months to more than 5 years following the stroke event (Lennon et al. 2008; Marzolini et al. ‘The Feasibility of Cardiopulmonary Exercise Testing for Prescribing Exercise to People after Stroke’ 2012; Tang et al. 2010). Although studies have demonstrated that cardiovascular fitness and mobility can improve as a result of interventions introduced in the chronic stage of stroke (Wade et al. 1992; Green et al. 2002; Tang et al. 2010; Brazzelli et al. 2011), no study to our knowledge, has contrasted the effects of an adapted CR intervention in the earlier chronic phase (3 months to 1 year) to the more remote chronic stage (>1 year following stroke).

Determining if there are greater benefits to be derived from referring patients earlier after stroke (i.e. within 1 year), and if a CR intervention results in ancillary benefits in addition to improvements in \( \dot{V}O_2^{peak} \), will have important implications to best practice guidelines if CR is to become a standard of care treatment following TSR. The purpose of this study was to evaluate physiological effects of a 24-week CR program in individuals with motor impairments following stroke, and examine group differences between participants <1 year vs. >1 year post-stroke. We hypothesized that a 6-month CR program would result in significant improvements in the primary outcome measures of ambulatory capacity, paretic-side leg extension isometric strength,
timed sit-to-stand performance, and \( \dot{VO}_{2}\text{peak} \) independent of time from stroke to commencement of the exercise program.

### 4.3 Subjects and Methods

Patients were referred to Toronto Rehabilitation Institute’s Risk Factor Modification and Exercise Program following Stroke (TRI-REPS) from outpatient stroke rehabilitation programs, primary care physicians, and from the community. The TRI-REPS program is a substream of the Institute’s cardiac rehabilitation program. Consecutively enrolled participants ≥12 weeks post-stroke with a stroke-related motor impairment score of <7 on the Chedoke-McMaster Stroke Assessment scale (CMSA) of at least one of arm, hand, leg, or foot were approached for participation in this study. A score of 1 indicates flaccid paralysis, 3 describes marked spasticity and weakness, 6 indicates near normal coordination of patterns of movement and no spasticity, and 7 describes normal movement (Gowland et al. 1993). All participants were able to ambulate ≥10 meters independently with/without an assistive device with no significant limitations due to pain, and were excluded if they had other neurological conditions, contraindications to maximal exercise testing such as severe aortic stenosis, significant cardiac arrhythmia, or uncontrolled resting severe hypertension (ACSM 2009). Individuals with little to no neurological deficits were integrated into the regular CR program and were not included in the analysis. The study was approved by the institution’s Research Ethics Board.

#### 4.3.1 Intervention: Adapted Cardiac Rehabilitation Program

The TRI-REPS service for stroke patients is similar in design to the traditional CR program (Tang et al. 2010; Hamm and Kavanagh 2000). Patients attended a 90 minute exercise class 1 time-wk\(^{-1}\) for 6 months. Nutrition and psychosocial counseling, education sessions, cardiac exercise assessments, and plasma glucose and lipid monitoring were offered. The case manager prescribed an individualized aerobic training (AT) program in the first weekly session, followed by a resistance training (RT) program in the following session. Patients were advised to complete 4
additional AT and 1-2 RT sessions at home, and these were tracked via exercise diary. All patients were prescribed a range of motion and flexibility routine carried out in class and at home.

Walking, elliptical, stationary recumbent or upright cycling were the modes of AT prescribed depending on individual ability and access to equipment in the community. The AT prescription was based on results of the cardiopulmonary exercise test conducted at entry and following 6 months of participation. The goal was to progress patients to 20-60 minutes of exercise (Gordon et al. 2004), 5 times-wk\(^{-1}\) (Hamm and Kavanagh 2000) at an intensity considering a combination of the following: 40-70% of heart rate reserve or \(\text{VO}_{2\text{peak}}\) (Gordon et al. 2004) the heart rate achieved at the gas exchange ventilatory anaerobic threshold (VAT) (Gordon and Scott 1995) determined by a combination of the V-slope method and the ventilatory equivalents methods (Beaver, Wasserman and Whipp 1986; ATS 2003), and/or a rating of perceived exertion of 11-16 (“light” to “hard”) on the Borg 6-20 Scale (Borg 1982). Interval training, characterized by short periods of increased exercise intensity alternating with longer periods of lower intensity exercise, was prescribed to patients when a faster speed did not preclude safety.

The choice and number of RT exercises were based on the patients’ goals, gait pattern, grip strength, joint range-of-motion, degree of hypertonicity, and balance. The exercises aimed to be functional and task-specific in nature, incorporating muscle actions that are performed during daily activities, targeting movement deficits and emphasizing re-training of balance, coordination, bearing and shifting weight, and incorporating multi-joint movements. Resistance was provided by hand-held dumbbells, exercise bands (wrist/ankle attachments), or patients’ body weight. A weight load equivalent to 50-60% of 1-repetition maximum was prescribed on the non-affected limb. On the paretic-side limb, \(\geq 50\%\) of 1-repetition maximum and/or a resistance rated as 13-14 on the rating of perceived exertion scale on the last repetition of the set was prescribed (Marzolini et al. 2008). Initially, participants performed 1 set of 10 repetitions of each exercise. They were gradually progressed to 2 sets, and then to 15 repetitions, before the resistance was increased (between 1.6-5 kg or to the next exercise band level) and repetitions reduced back to 10, after which the process repeated again.
4.3.2 Testing Procedures

**Primary outcomes**

Functional ambulation was measured by the 6-Minute Walk distance (6MWD) test, which measures the distance that an individual can quickly walk in a period of 6 minutes on a flat surface. The test was performed on a 30-metre course at baseline and following 6 months of training that was marked every 3 metres. The turnaround point was marked with a cone. Standardized instructions were given (ATS 2002) to walk as great a distance as possible during the allotted time without jogging. Patients were permitted to use their walking aids. Standardized encouragement was given every 30 seconds, and the time remaining was called every two minutes. Distance walked was measured to the nearest metre. At baseline, participants completed two 6MWD tests (Solway et al. 2001) on the same day, with 15 minutes rest between trials. The longest distance of each of the two trials was recorded. Results were reported according to percentage of predicted norms (Enright and Sherrill 1998).

A symptom-limited exercise test was performed on a recumbent cycle ergometer with specialized pedals to secure feet (Ergoline Select 1000, Germany) or upright cycle (Ergoselect 200P, Germany), or a treadmill. The type of ergometer was chosen based on balance, and ability to control the leg/foot position in pedals. Work load on the cycle ergometer was increased by either 8.3 or 16.7 Watts every minute. On the treadmill, the initial walking speed was one that was comfortable, and subsequently the pace was increase by half a mile per hour every 30 seconds until a maximum comfortable walking speed was achieved. Then the incline of the belt was increases by 1% every 30 seconds to peak effort. Breath-by-breath gas samples were collected via calibrated metabolic cart (SensorMedics Vmax Encore, California) to determine peak oxygen uptake (\(\dot{V}O_2\text{peak}\), mL·kg\(^{-1}\)·min\(^{-1}\)). Twelve-lead electrocardiogram (ECG) (Marquette Case 80) and rating of perceived exertion (6-20 scale) was monitored continuously. Blood pressure was measured at baseline and every 2 minutes thereafter. A resting 12-lead ECG, medical history, and anthropometric measures were collected prior to each cardiopulmonary exercise test.
Two 3-second trials of maximal isometric knee extension force were measured with a hand-held force gauge dynamometer (Chatillon-Ametek, DFE-500 Largo, FL, USA). The subjects were seated with limb placed at a 30-degree joint angle from vertical, as measured by goniometer. The dynamometer was applied immediately above the malleoli and perpendicular to the tibial crest for knee extension. Two minutes of rest separating each trial on the same side was performed. The highest force generated over the 2 trials was recorded. The reliability and precision of hand-held dynamometer measurements has been established for patients with stroke (Bohannon 1990; Eng, Kim and MacIntyre 2002; Hammer and Lindmark 2003). Peak force was calculate as a percentage of body mass (Jaric 2002).

For the timed repeated sit-to-stand test, standardized instructions were provided to stand fully from a 43-cm-high chair 5 times as quickly as possible, and not to touch the back of the chair during each repetition. The faster time of two trials was recorded. Two minutes rest was allowed between trials. This test has been shown to have excellent intrarater, interrater, and test-retest reliability in individuals in the chronic stage of stroke (Whitney et al. 2005; Mong, Teo and Ng 2010).

**Secondary Outcomes**

Perceived participation was measured by the Stroke Impact Scale 3.0 (SIS) questionnaire. The SIS is an instrument that combines disability and health-related quality of life (HRQoL) dimensions into a self-report questionnaire (Duncan et al. 2001). This instrument measures the impact of stroke in 8 domains of recovery and the participation domain can be analyzed separately (Duncan et al. 1999). This scale is interview-administered and has been shown to have excellent test-retest reliability (Duncan et al. 1999). The domain of perceived participation was of particular interest as it represents re-integration into social and community activities and measures the impact of stroke on work, social activities, quiet recreations, active recreations, role as a family member, ability to help others, religious activities and life control. Only the data from this domain was used. The score was calculated into a percentage (0-100) according to Duncan et al. with low values representing restricted participation (Duncan et al. 1999).
Gait parameters (speed and spatial characteristics) were assessed using a 5-metre-long pressure-sensitive mat (Gait-Rite Mat, CHR Inc.). Standby supervision was provided by two staff members, but no physical assistance was provided. Three trials of the fastest possible speed at which the individual felt safe were conducted and the average was calculated. Three meters was provided at each end of the mat to account for acceleration and deceleration, such that the total distance walked was 11 meters but only the middle 5 meters were timed. All subjects used the gait aids prescribed to them. Cadence was measured in steps per minute, paretic and non-paretic step length was measured as the heel-heel distance.

The Berg Balance Scale is a validated (Berg et al. 1992) 14-item scale designed to measure balance with excellent reliability in individuals with stroke (Blum and Korner-Bitensky 2008). Each task is rated on a scale of 0 to 4, with a maximal score of 56, where higher scores indicate better balance. A score of 42 or lower on the Berg Balance Scale is reported as the single best predictor of multiple or injurious falls in people following stroke (Tilson et al. 2012).

Range of motion (ROM) for maximal shoulder flexion (arm straight and leading with thumb in a standing position) and hip flexion (raising knee from standing position while supported), using an inclinometer (J-Tech Medical Dualer) that was calibrated at each trial. Two trials on each side were performed, with the greater ROM noted.

Two 3-second trials of maximal isometric elbow flexion force were measured with a hand-held force gauge dynamometer at 30 degrees elbow flexion and hand supinated. The dynamometer was placed at the front of the forearm one inch proximal to the wrist crease. The patient was positioned in standing with back against a wall. A second tester ensured that only the forearm moved during testing to prevent facilitation from other muscle groups. Peak force was calculated as a percentage of body mass.

Maximal 5-second isometric grip force was measured by a handgrip dynamometer (JAMAR, Jackson, MI), with elbow positioned in full extension. Two trials were performed, with 1 minute of rest between trials. The higher score was recorded. The reliability and precision of handgrip
dynamometer measurements has been established for individuals with stroke (Bohannon 1990; Eng, Kim and MacIntyre 2002; Hammer and Lindmark 2003).

VAT was determined by a combination of the V-slope method and the ventilatory equivalents methods (Beaver, Wasserman and Whipp 1986; ATS 2003). The V-slope method was defined as the point of departure from linearity of carbon dioxide output plotted against oxygen uptake. The ventilatory equivalent method was defined as the level corresponding to the rise in ventilatory equivalent of oxygen that occurs without a concurrent rise in the ventilatory equivalent of carbon dioxide. The VAT is considered a valid measure demonstrating high reproducibility and low interobserver variability when established standards are followed (Sullivan and Cobb 1990; Meyer et al. 1996).

4.3.3 Analysis

Data are presented as mean ± SD unless otherwise indicated. Change from baseline was expressed as a percentage and calculated as [(Post-CRP score – Pre-CRP score) / Pre-CRP score] * %. To examine differences between subgroups of participants the sample was dichotomized by median split to create earlier and later entry groups (≤1/>1 year post-stroke respectively). The median split was used to define the group membership of time to enrollment as it was less sensitive to the “time from stroke” outliers. Differences between the subgroups at baseline were assessed using independent samples Student’s t tests for continuous variables and $X^2$ tests for categorical variables. Student’s t test for paired samples was used to determine within group changes from baseline to post training. Between group differences were analyzed by using analysis of variance (ANOVA). A Bonferroni correction was used to adjust for multiple comparisons for primary outcome measures. A level of p<0.006 was considered statistically significant for primary measures. Probability values <0.05 were considered significant for secondary outcome measures. All analyses were performed in SPSS (version 19.0, SPSS, Inc., Chicago, IL).

4.4 Results

4.4.1 Baseline characteristics
Of the 131 patients referred to TRI-REPS, 91.6% (n=120) completed the program (91.5% and 91.7% from the early and later entry groups, respectively). There was no significant difference between participants who did or did not complete the program with respect to age (p=0.4), sex (p=0.4), time from stroke (p=0.5), or CMSA score of hand, arm, leg or foot (all p>0.05). For the 120 subjects who completed the program, subject characteristics are presented in Table 4.1 and 4.2. At baseline, those who were referred ≤1 year post-stroke had greater affected knee extension isometric strength, a smaller waist circumference, and were more likely to be prescribed a calcium channel blocker medication than those referred >1 year post-stroke (Table 4.1).

**Table 4.1. Baseline Characteristics by Stroke Recovery Time**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients N=120</th>
<th>≤1Yr Post Stroke N=65</th>
<th>&gt;1Yr Post Stroke N=55</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, male n (%)</td>
<td>85 (70.8)</td>
<td>45 (69.2)</td>
<td>40 (72.7)</td>
<td>0.7</td>
</tr>
<tr>
<td>Age, years (range)</td>
<td>63.8±12.7 (27-88)</td>
<td>63.7±13.4</td>
<td>64±11.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Time post-stroke, weeks (range)</td>
<td>101.5±169.3 (12-1460)</td>
<td>33.7±11.8 (12-52)</td>
<td>181.7±224.2 (56-1460)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist Circumference, cm</td>
<td>98.8±13.4</td>
<td>96.5±12.9</td>
<td>101.6±13.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Ischemic/Hemorrhagic/Unknown stroke type, n (%)</td>
<td>84(70)/33(27.5)/3(2.5)</td>
<td>42(64.6)/22(33.8) /1(1.5)</td>
<td>42(76.4)/11(20) /2(3.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Right/Left/Bilateral hemisphere affected, n (%)</td>
<td>51(42.5)/65(54.2)/3(2.5)</td>
<td>28(43.1)/36(54.4) /1(1.5)</td>
<td>23(41.8)/29(52.7)/2 (3.6)</td>
<td>0.7</td>
</tr>
<tr>
<td>Coronary Artery Disease, n (%)</td>
<td>28 (23.3)</td>
<td>14(21.5)</td>
<td>14(25.5)</td>
<td>0.6</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>34 (28.3)</td>
<td>20(30.8)</td>
<td>14(25.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>73 (60.8)</td>
<td>43 (66.2)</td>
<td>30 (54.5)</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
<td>p-value</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Atrial Fibrillation, n (%)</td>
<td>21 (17.5)</td>
<td>10 (15.4)</td>
<td>11 (20)</td>
<td>0.5</td>
</tr>
<tr>
<td>Medications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>41 (34.2)</td>
<td>23 (35.4)</td>
<td>18 (32.7)</td>
<td>0.8</td>
</tr>
<tr>
<td>Ca²⁺-channel antagonists</td>
<td>31 (25.8)</td>
<td>22 (33.8)</td>
<td>9 (16.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Other Antihypertensives</td>
<td>82 (68.3)</td>
<td>47 (73.4)</td>
<td>35 (63.6)</td>
<td>0.3</td>
</tr>
<tr>
<td>Lipid lowering agents</td>
<td>93 (77.5)</td>
<td>52 (80)</td>
<td>41 (74.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>Gait aids,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/Cane/Rollator/wc, n (%)</td>
<td>46(39)/43(36.4)/26(22)/1(1.8)</td>
<td>24(38.1)/23(36.5)/16(25.4)</td>
<td>22(40)/21(38.2)/11(20)/1(1.8)</td>
<td>0.7</td>
</tr>
<tr>
<td>CMSA scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm</td>
<td>4.2±1.6 (1-7)</td>
<td>4.2±1.6 (1-7)</td>
<td>4.2±1.7 (2-7)</td>
<td>0.97</td>
</tr>
<tr>
<td>Hand</td>
<td>4.3±1.8 (1-7)</td>
<td>4.2±1.8 (1-7)</td>
<td>4.3±1.8 (2-7)</td>
<td>0.7</td>
</tr>
<tr>
<td>Leg</td>
<td>5.0±1.2 (2-7)</td>
<td>5.1±1.1 (2-7)</td>
<td>4.9±1.3 (3-7)</td>
<td>0.4</td>
</tr>
<tr>
<td>Foot</td>
<td>4.2±1.7 (1-7)</td>
<td>4.3±1.6 (1-7)</td>
<td>4.1±1.7 (2-7)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

CMSA=Chedoke-McMaster Stroke Assessment Scores

Values are mean±SD unless otherwise indicated.
4.4.2 Objective 1: Physiological and Psychosocial Changes after 6 Months of Exercise Training

Primary outcomes:

Among all patients, there were significant improvements in 6MWD (15.3±21.2%), repeated sit-to-stand performance (11.8±26.6%), affected isometric knee extension peak force as % of body mass (22.1±35.7%) and \( \dot{\text{VO}}_{2\text{peak}} \) (16±21.3%) (Table 4.2).

Secondary outcomes:

There were significant improvements in 5 meter fast-paced walking speed (18.8±26.9%), cadence (10.9±13.4%), paretic and non-paretic-side step length (7.6±27.8 and 6.5±19.1% respectively), and affected-side grip strength (37.4±82.8%), VAT (12.3±18.7%), affected-side elbow flexion peak force relative to body mass (28.6±51%), affected-side shoulder and hip flexion ROM (10.5±37.9% and 11±26.1%), Berg balance score (6.0±10.8%), and participation/social reintegration (15.5±41.6%) (Table 4.2).

4.4.3 Objective 2: Effects of Stroke Recovery Time

Within-Group Changes

There were 65 subjects who were enrolled in the CRP < 1 year post-stroke, and 55 enrolled > 1 year post-stroke. Both earlier and later entry groups demonstrated significant improvements in 6MWD (20.6±22.2 vs. 9.9±18.8% respectively), timed repeated sit-to-stand performance (11.9±29.3 vs. 11.7±23.4%), \( \dot{\text{VO}}_{2\text{peak}} \) (16.9±24 and 14.0±17.5%) and affected-side isometric knee extension strength (20.8±38.2 vs. 23.6±32.7%) (all p<0.001) (Table 4.2).

Both earlier and later entry groups had significant improvements (p<0.05) in VAT (9.3±18.3 and 17.2±18.7%), 5-meter fast walk speed (25.3±30.3 and 12.1±21.3%), cadence (12.8±13.9 and 8.9±12.7%), affected elbow isometric flexion peak strength (22.3±47.4 and 35.7±54.8%), affected-side grip strength (38.7±85.1 and 35.8±81.1%), affected-side shoulder flexion ROM (13.6±30.2 and 9.2±30.0%), Berg Balance Scale score (7.5±9.9 and 4.3±11.6%), and perceptions of physical recovery and participation (23.4±47.2 and 19.7±37.4%) (Table 4.2). The early entry, but not late entry group had significant improvements in affected hip ROM (12.4±22.6 and...
9.2±30%), paretic-side step length (12.2±36.7 and 2.9±13.2%) and non-paretic side step length (12.1±19.2 and 0.8±17.6%).

**Between-Group Differences**

There were significantly greater improvements in those who started exercise ≤1 year post-stroke compared to >1 year post stroke in 6MWD (p=0.004), nonparetic-side step length, (p=0.007) and maximal walking speed (p=0.04) (Table 4.2). Paretic-side leg strength remained significantly higher at 6 months in the early entry group than in the later entry group (32.7±11.1 vs. 27.3±10.2 kg of force, % of body mass respectively, p=0.009).

**Table 4.2. Absolute Physiological and Psychosocial Measures at Baseline and Change from Baseline by Stroke Recovery Time**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients n=120</th>
<th>≤1Yr Post-Stroke (n=65)</th>
<th>&gt;1Yr Post-Stroke (n=55)</th>
<th>P Value for Group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Mass Index, kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>27.3±5.1</td>
<td>27.2±5.1</td>
<td>27.6±5.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Change from Baseline (p value)</td>
<td>0.6±1.6 (0.7)</td>
<td>0.13±1.2 (0.4)</td>
<td>-0.02±2.0 (0.9)</td>
<td>0.6</td>
</tr>
<tr>
<td>Six Minute Walk Distance, metres</td>
<td>n=75</td>
<td>n=38</td>
<td>n=37</td>
<td></td>
</tr>
<tr>
<td>Baseline (% predicted)</td>
<td>283.2±126.6</td>
<td>294.7±119.7</td>
<td>271.5±134</td>
<td>0.4</td>
</tr>
<tr>
<td>Change from Baseline (p value)</td>
<td>37.5±48.4 (&lt;0.001)</td>
<td>52.9±49.5 (&lt;0.001)</td>
<td>21.7±42.3 (p=0.004)</td>
<td>0.004</td>
</tr>
<tr>
<td>Repeated Sit-to-Stand Time, seconds</td>
<td>16.3±9.5</td>
<td>16.7±10.7</td>
<td>15.9±8.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Change from Baseline (p value)</td>
<td>-3.0±7.0 (&lt;0.001)</td>
<td>-3.5±8.2 (0.001)</td>
<td>-2.4±5.3 (0.002)</td>
<td>0.4</td>
</tr>
<tr>
<td>Peak Oxygen Uptake, mL·kg⁻¹·min⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (% age, sex predicted norms)</td>
<td>15.2±4.5 (64.3±25.9)</td>
<td>15.6±4.6 (67.1±26.6)</td>
<td>14.8±4.4 (61.3±25)</td>
<td>0.3</td>
</tr>
<tr>
<td>Change from Baseline (p value)</td>
<td>2.0±2.8 (&lt;0.001)</td>
<td>2.3±3.3 (&lt;0.001)</td>
<td>1.6±2.1 (&lt;0.001)</td>
<td>0.3</td>
</tr>
<tr>
<td>Measure</td>
<td>Baseline</td>
<td>Baseline</td>
<td>Baseline</td>
<td>p value</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td>Knee Extension Isometric Strength, Affected-Side (kg force as % body mass)</td>
<td>25.9±10.1</td>
<td>28.5±10.2</td>
<td>22.9±9.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Change from Baseline (p value)</td>
<td>4.3±6.7 (&lt;0.001)</td>
<td>5.2±6.9 (&lt;0.001)</td>
<td>4.4±6.5 (&lt;0.001)</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grip Strength, Affected-Side (kg)</td>
<td>15.4±14.9</td>
<td>15.5±16.4</td>
<td>15.3±12.5</td>
<td>0.95</td>
</tr>
<tr>
<td>Change from Baseline (p value)</td>
<td>2.0±5.0 (&lt;0.001)</td>
<td>2.2±5.0 (0.001)</td>
<td>1.7±5.0 (0.02)</td>
<td>0.6</td>
</tr>
<tr>
<td>Elbow Flexion Isometric Strength, Affected-Side (kg force as % body mass)</td>
<td>10.9±6.9</td>
<td>11.3±7.3</td>
<td>10.5±6.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Change from Baseline (p value)</td>
<td>2.0±4.7 (&lt;0.001)</td>
<td>1.3±5.0 (0.04)</td>
<td>2.8±4.1 (&lt;0.001)</td>
<td>0.1</td>
</tr>
<tr>
<td>Ventilatory Anaerobic Threshold, mL·kg⁻¹·min⁻¹</td>
<td>N=72</td>
<td>N=45</td>
<td>N=27</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.9±3.6</td>
<td>13.2±3.7</td>
<td>12.4±3.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Change from Baseline (p value)</td>
<td>1.3±2.1 (&lt;0.001)</td>
<td>1.1±2.2 (0.003)</td>
<td>1.8±1.9 (&lt;0.001)</td>
<td>0.1</td>
</tr>
<tr>
<td>Gait Parameters, 5 meter Fast Walk Speed (cm·sec⁻¹)</td>
<td>n=71</td>
<td>N=36</td>
<td>N=35</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>91.3±40.6</td>
<td>98.1±41.4</td>
<td>84.4±39.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Change from Baseline (p value)</td>
<td>14.5±21.7 (p&lt;0.001)</td>
<td>19.6±25.9 (p&lt;0.001)</td>
<td>9.3±15.0 (p=0.001)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cadence, steps/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>100.2±26.1</td>
<td>104.9±28.5</td>
<td>95.4±22.8</td>
<td>0.1</td>
</tr>
<tr>
<td>Change from Baseline (p value)</td>
<td>10.2±12.6 (p&lt;0.001)</td>
<td>11.9±13.7 (p&lt;0.001)</td>
<td>8.4±11.4 (&lt;0.001)</td>
<td>0.3</td>
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<td>--------------------------------</td>
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</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Change from Baseline (p value)</td>
<td>Baseline</td>
<td>Change from Baseline (p value)</td>
</tr>
<tr>
<td></td>
<td>53.3±15.1</td>
<td>2.6±9.7 (p=0.03)</td>
<td>51.2±15.8</td>
<td>3.1±8.8 (p=0.004)</td>
</tr>
<tr>
<td></td>
<td>55.7±15.8</td>
<td>4.2±11.7 (0.04)</td>
<td>51.6±17</td>
<td>5.9±8.9 (&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>51.0±14.1</td>
<td>0.87±6.7 (0.5)</td>
<td>50.9±14.7</td>
<td>0.3±7.8 (0.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.7</td>
</tr>
</tbody>
</table>
Values are mean±SD unless otherwise indicated

4.5 Discussion

A cardiac rehabilitation program (CRP) can successfully be adapted to suit those with impairments post-stroke and yield benefits beyond the previously reported improvement in cardiovascular fitness. Specifically, we demonstrated that a CRP of AT and RT yielded significant gains in functional ambulation, sit-to-stand performance, affected-side leg extension isometric peak force, as well as cardiovascular fitness. Exploring a range of functional and HRQoL measures suggested a significant improvement in balance, affected-side shoulder and hip range of motion, affected-side grip and elbow flexion isometric peak force, VAT, perceptions of participation/social reintegration, and fast-paced gait characteristics including walking speed, cadence, paretic and non paretic step lengths. In a dichotomous examination of stroke recovery time, better outcomes for ambulatory performance (6MWD, fast-paced walking speed, and non paretic step length), occurred for those starting CRP earlier (≤1 year following stroke, earlier entry group), compared to those staring CRP later (>1 year post-stroke, later entry group).

Ambulation and sit-to-stand performance are biomechanically demanding activities that are performed every day (Berger et al. 1988). These are crucial activities for resuming independence and are often impaired post-stroke (Lomaglio and Eng 2004; Gresham et al. 1975). In the current study, the significant improvement in 6MWD of 37.5 meters was beyond the threshold of 29 meters reported as the minimal detectable change (MDC) in people within 1 year from stroke (Liu et al. 2008; Eng, Dawson and Chu 2004) but less than the MDC of 54.1 meters measured in people who were a mean of 33.7 days post stroke (Fulk, Echternach and O'Sullivan 2008). This discrepancy between MDCs suggests that MDC may be context-specific, and stroke recovery time may be an important source of variation to the MDC as performance may be less variable the longer the time from stroke.

Also, the improvement in sit-to-stand performance of 3 seconds observed in the current study was similar in magnitude to the significant change of 4 seconds observed in a previous study that included 12 weeks of high intensity RT in patients 2 years post-stroke (Weiss et al. 2000).
However, without a control group interpretation of these changes should be made with caution. Conversely, another trial that included post-stroke AT only (with no RT component) reported only modest improvements in sit-to-stand time that was comparable to the control group (2.4 seconds and 0.1 seconds, respectively, p=0.1 between groups) (Globas et al. 2012). This suggests that RT may be an important adjunct to AT for improving functional outcomes, such as timed sit-to-stand performance. Indeed muscular strength has been positively associated with performance of activities-of-daily-living including walking and sit-to-stand performance (Canning, Ada and O'Dwyer 2000; Morris, Dodd and Meg 2004), and the addition of RT is predominantly responsible for change in muscular strength (Marzolini, Oh and Brooks 2012; Marzolini et al. 2008; Morris, Dodd and Meg 2004). While AT also contributes to improved functional ambulation through augmented cardiovascular fitness, gait economy, and oxidative capacity of peripheral muscles following stroke (Macko et al. 2005), the effects of AT in stroke recovery might be intensified with the addition of RT. However, while meta-analyses comparing AT vs. control and AT+RT vs. control in people post-stroke show both exercise interventions result in improvements in mobility and other parameters of stroke recovery, these interventions have rarely been compared directly (Brazzelli et al. 2011; Brazzelli et al. 2012). To our knowledge, only one study has compared combined AT+RT with AT alone in individuals following stroke, and while underpowered showed a two fold greater increase in 6MWD with combined training compared to AT alone (n/s) (Lee et al. 2008).

Nevertheless, AT and RT modalities are standard of care exercise interventions offered in CRPs (ACSM 2009), and in combination may have contributed to the improvements demonstrated over multiple dimensions of stroke recovery in the current study. Indeed, two of the factors identified as positively associated with better functional ambulation, and sit-to-stand performance in the literature— greater paretic-side leg strength and cardiovascular fitness— improved in the current study. Additionally, the mean increase in $\dot{V}O_{2\text{peak}}$ (mL·kg$^{-1}$·min$^{-1}$) of 16% was similar in magnitude to improvements reported in individuals in the chronic stroke phase randomized to exercise interventions (10.7% to 17%) (Lennon et al. 2008; Potempa et al. 1995; Pang et al. 2005; Macko et al. 2005), that exceeded changes observed in the respective control groups. AT and RT interventions are usually minimal or absent in TSR programs and these data underscore the benefits of referring individuals to CRPs following completion of TSR.
In the current study, there was also a significant and clinically meaningful (Duncan et al. 1999) improvement in perceived participation. Perceived participation (a domain of HRQoL) has been reported to be a predictor of global recovery (Duncan et al. 1999) and to be positively associated with paretic-side leg muscle strength and walking ability measured by the 6MWD (Flansbjer, Downham and Lexell 2006; Danielsson, Wille´n and Sunnerhagen 2011). In fact Mayo et al. reported that 6MWD was the only significant determinant of integration into the community in those 1 year post-stroke (Mayo et al. 1999). The positive association between perceived participation/social integration and physiological parameters associated with AT and RT interventions was highlighted in a recent meta-analysis that reported that only studies that included a combined RT and AT intervention had a significant effect on HRQoL post-stroke with no change as a result of studies that included AT alone (Chen and Rimmer 2011). These findings, along with the results of the current study, highlight the importance of the combined treatment approach of a CRP for affecting clinically meaningful change.

The changes observed in the remaining secondary outcomes measured in the present study provide further evidence that the 6-month intervention was effective for improvements over multiple dimensions of stroke recovery. We observed a significant improvement in 5 meter fast-paced gait speed of 15 cm·second\(^{-1}\) which was beyond the MDC of 10 cm·second\(^{-1}\) and 9% change reported by Hiengkaew et al. and Faria, et al. respectively for individuals in the chronic phase of stroke (Hiengkaew, Jitaree and Chaiyawat 2012; Faria et al. 2011). Moreover, cadence, and paretic and nonparetic-side step length improved significantly. These results are congruent with a study conducted by Patterson et al. in which improvement was observed in preferred walking pace velocity, cadence and bilateral step length after 6 months of treadmill training in individuals in the chronic stroke phase (Patterson et al. 2008). In addition, the 12% change in the VAT in the present study was similar in magnitude to relative gains experienced by individuals following a cardiac event participating in an exercise program (2-11%) (Milani, Lavie and Mehra 2004; Marzolini et al. 2008; Carlson et al. 2000; Lavie and Milani 200). We also showed significant gains in paretic-side shoulder and hip range of motion, and paretic-side grip and elbow flexion strength. While balance, as measured by the Berg Balance Scale improved significantly, the 6% change was just under the MDC of 10% (Hiengkaew, Jitaree and
However, there was a significant reduction of 37.1% in the proportion of patients who scored at or below the level reported as the single best predictor of multiple or injurious falls (i.e. ≤42/56 on the Berg Balance Scale) (Tilson et al., 2012).

The results of this study help to further elucidate patterns of exercise responsiveness in the chronic stage of stroke. This issue merits attention as patients are typically referred to CRPs remote from their stroke event after having received all of the TSR available to them. Studies examining the natural history of recovery in mobility suggest that while there may be a plateau in recovery 3-6 months following stroke (time to plateau can vary by stroke severity) (Kelly-Hayes et al. 1989; Jorgensen et al. 1995; Wade et al. 1992), mobility status deteriorates in 20%-43% of patients 1 to 3 years post-stroke (van de Port et al. 2006; Paolucci et al. 2001). This pattern of diminishing recovery also extends to HRQoL benefit. Duncan et al. have reported that HRQoL improvements as measured by the SIS instrument improve 1 to 3 months following stroke with little change from 3 to 6 months (Duncan et al. 1999). Nonetheless, we observed that people more than 1 year post-stroke had significant improvements in 6MWD, sit-to-stand performance, paretic-side knee extension strength, \( \dot{V}O_{2\text{peak}} \), HRQoL (perceived participation), VAT, balance, paretic-side grip and elbow flexion strength, paretic-side shoulder range of motion, and fast-paced walking speed and cadence, despite the conventional belief of an early recovery plateau.

Conversely, there was a diminished ability of the later entry group to adapt to the same exercise program when compared to the earlier entry group in relation to functional ambulation, walking speed, and non-affected side step length during the gait cycle. Poorer paretic-side leg strength may have disadvantaged the later entry group in achieving equivalent gains in functional mobility compared to the earlier entry group. Several studies have shown that muscular strength is correlated with walking speed, independence and distance in patients following stroke (Morris, Dodd and Meg 2004), although correlation does not imply causation. Specifically, paretic-side leg muscle strength has been reported to be a stronger predictor of gait performance than non-paretic-side leg strength, explaining up to 50% of the variance in gait performance (Flansbjer, Downham and Lexell 2006; Hsu, Tang and Jan 2003). While there were significant and similar improvements in paretic-side leg strength for the earlier and later entry groups in the current study, strength remained significantly lower in the later entry group post-training and may have mitigated their ability to improve gait speed and ambulation endurance. This suggests that 6
months of exercise training may not make up for the deterioration in paretic-side leg strength that occurs with time. Therefore, starting an exercise program early post-stroke may mitigate or counteract the deterioration in paretic-side leg strength and allow for greater ambulatory related adaptation to exercise. However, leg strength may not be as powerful a predictor of change in other outcomes. For example, earlier and later entry groups experienced similar and significant improvements in sit-to-stand performance. Recent evidence suggests that sit-to-stand performance, while affected by muscular strength, is more related to balance in patients with chronic stroke (Ng 2010).

Adding to the evidence elucidating patterns of stroke recovery in ambulation, a recent study conducted by Duncan et al. showed consistent patterns of adaptation to training in patients in the earlier chronic stage of recovery (Duncan et al. 2011). Patients randomized to receive AT either at 2 months or 6 months post-stroke experienced similar and significant improvements in 6MWD to each other. The earlier interventions (≤6 months post stroke) may not have allowed for the deterioration in paretic-side leg strength observed in the later entry group (>1 year post-stroke) of the current study and would not have posed a limitation to either group. Future studies are needed to examine the underlying causal pathways leading to change in muscular strength, ambulation and gait characteristics throughout the stages of chronic stroke recovery and consequence on adaptation to exercise.

4.6 Limitations

This study has several limitations. With regard to design, causal conclusions regarding the impact of a CRP on outcomes cannot be drawn from this observational study that did not include a non exercising control group. Also, there may be unmeasured factors that contributed to observed differences between the earlier and later entry groups. Moreover, the sample was not large enough to analyze differences between those referred over multiple time spans from index stroke event. Instead, we used a median split to determine a dichotomous group comparison. Finally, some measures were not conducted on all patients. Our analyses encompassed a real-world out-patient population referred to a CRP, suggesting results may be more generalizable to the clinical population.
4.7 Conclusions

This study demonstrated that persons living with the effects of a stroke enrolled in a 24-week CR program of aerobic and resistance training showed improvements in physiological and psychosocial parameters. While both those referred ≤1 year and >1 year post-stroke benefit from CR, those who start CR earlier have greater benefits in some parameters of mobility. These findings are of particular importance given that patients are typically referred to CRP remote from their stroke event and challenge the conventional belief of an early recovery plateau.

4.8 Acknowledgements:

We acknowledge the contribution of Susie Ward and patients and staff at Toronto Rehab
Chapter 5 THE EFFECTS OF AN AEROBIC AND RESISTANCE EXERCISE TRAINING PROGRAM ON COGNITION FOLLOWING STROKE

Accepted for publication in Neurorehabilitation and Neural Repair (Marzolini, S., Oh, P.I., McIlroy, W.E., Brooks, D. Neurorehabil Neural Repair)

Susan Marzolini was Case Manager for the patients of this study and prescribed the aerobic and resistance training components as well as progression of exercise to each patient. Susan Marzolini also conceived and designed the research with Dr. Brooks, acquired the data, analysed and interpreted the data, performed statistical analysis and drafted the manuscript.

5.1 ABSTRACT

**Background:** Cognitive benefits obtained from exercise in healthy populations support the idea that aerobic and resistance training (AT+RT) would confer benefit for post-stroke recovery. However, there is little evidence regarding the effectiveness of such programs.

**Objective:** To evaluate the effects of a 6 month exercise program of AT+RT on cognition in consecutively enrolled patients with motor impairments ≥10 weeks post-stroke.

**Methods:** Outcomes were measured before and after 6 months of AT+RT on 41 patients. Cognition was measured by the Montreal Cognitive Assessment (MoCA). Secondary measures included gas exchange ventilatory anaerobic threshold (VAT), body composition by dual energy x-ray absorptiometry, and depressive symptoms by questionnaire.

**Results:** There were significant improvements in overall MoCA score (22.5±4.5 to 24.0±3.9, p<0.001) and in the subdomains of attention/concentration (4.7±1.7 to 5.2±1.3, p=0.03) and visuospatial/executive function (3.4±1.1 to 3.9±1.1, p=0.002). There was a significant reduction
in the proportion of patients meeting the threshold criteria for mild cognitive impairment at baseline compared to post-training (65.9% vs. 36.6%, p<0.001). In a linear regression model there was a positive association between change in cognitive function and change in fat-free mass (β=0.002, p=0.005) and change in attention/concentration and change in VAT (β=0.383, p=<0.001), independent of age, sex, time from stroke, and change in fat mass and depression score.

**Conclusion:** A combined training model (AT+RT) resulted in improvements in cognitive function and a reduction in proportion of patients meeting the threshold criteria for mild cognitive impairment. Change in cognition was positively associated with change in fat-free mass and VAT.

### 5.2 Introduction

Cognitive impairment, cardiovascular deconditioning and muscle weakness, are well established sequelae of stroke and contribute to the impairment that has made stroke one of the leading causes of serious, long-term disability in North America (Centre for Chronic Disease Prevention and Control, 2001, 2003, Gordon et al., 2004). Cognitive impairment occurs in up to 64% of people who have had a stroke (Ya-Ping et al. 2006) and has been associated with a 3-fold increase in risk for mortality (Hobson and Meara 2009), increased rates of institutionalization (Pasquini et al. 2007), and decreased ability to perform instrumental activities of daily living (Mok et al. 2004). Moreover, it places individuals who have had a stroke at a greater risk of developing dementia (Yip, Brayne and Matthews 2006). Data from older adult and animal models provide compelling evidence that exercise can improve cognition and promote neurogenesis (Farmer et al. 2004). In the healthy population, it is becoming increasingly evident that both aerobic training (AT) and resistance training (RT) have the potential to improve cognition. A meta-analysis of 18 studies showed that programs of both AT+RT resulted in significantly greater improvements in cognition than programs of AT alone (Colcombe and Dramer 2003). Recent evidence has linked brain atrophy and poor cognitive performance with reduced fat-free mass (muscle mass) in people with early Alzheimer disease (Burns et al. 2010) suggesting that exercise such as RT that provides an anabolic stimulus (Marzolini, Oh and Brooks 2012; Marzolini et al. 2008) may have the potential to ameliorate cognitive deficits.
However, few studies have examined the impact of an exercise program on cognition in individuals following a stroke, and the focus has largely been to examine the effect of AT alone (Rand et al. 2010; Quaney et al. 2009). Moreover, to our knowledge, no study has explored the association between change in cognition and change in fat-free mass as a result of an exercise training program.

Accordingly, the aim of this investigation was to evaluate the effects of a 6 month exercise program of AT+RT on cognition, and to explore associations between change in cognition and change in physiological outcomes attributed to AT (cardiovascular fitness) and RT (fat-free mass). We hypothesized that 6 months of AT+RT would result in a significant improvement in cognition and be positively associated with favorable change in submaximal cardiovascular fitness and muscle mass. Examining the benefits of a combined training approach (AT+RT) and the interaction between cognition and physiological outcomes would aid in selecting optimal treatment strategies for improving physiological and cognitive well-being post-stroke.

5.3 Methods

5.3.1 Participants

Patients were referred to Toronto Rehabilitation Institution’s Risk Factor Modification and Exercise Program following Stroke (TRI-REPS) from outpatient stroke rehabilitation programs, primary care physicians, and from the community. The TRI-REPS program is a substream of the Institution’s cardiac rehabilitation program. Consecutively enrolled patients ≥10 weeks post-stroke with a stroke-related motor impairment score of <7 on the Chedoke-McMaster Stroke Assessment scale of the arm, hand, leg, or foot (described below) were approached for participation in this study. All patients were able to ambulate ≥10 metres independently with/without an assistive device with no significant limitations due to pain, and were excluded if they had other neurological conditions, contraindications to maximal exercise testing such as severe aortic stenosis, significant cardiac arrhythmia, or uncontrolled resting severe hypertension (ACSM 2009). Only one patient declined to participate.
Outcome measures were conducted at baseline and following 6 months of exercise training in the same order. The Centre for Epidemiological Studies Depression (CES-D) Scale questionnaire was completed on the same day but prior to the cardiopulmonary exercise test. The Montreal Cognitive Assessment (MoCA) was conducted on a separate day prior to other assessments to avoid the effect of fatigue. On a subsequent visit, a dual energy x-ray absorptiometry (DXA) scan was conducted. The study was approved by the institution’s Research Ethics Board and written informed consent was obtained from all participants.

5.3.2 Adapted Cardiac Rehabilitation Program

The TRI-REPS service for stroke patients is similar in design to the traditional cardiac rehabilitation program (Hamm and Kavanagh 2000). Patients attended a 90 minute exercise class 1 time-wk^-1 for 6 months. Nutrition and psychosocial counseling, education sessions, cardiac exercise assessments, and plasma glucose and lipid monitoring were offered. The case manager prescribed an individualized AT program in the first weekly session, followed by an RT program in the following session. When the patient was ready to perform RT at home (typically after 2-3 supervised sessions), they were provided with a booklet including instructions for lifting weights safely, how to progress with the exercises, as well as pictures and a written description of each exercise. Patients were advised to complete 4 additional AT and 1-2 RT sessions at home. Patients were required to keep a detailed record of each exercise session, noting the precise distance walked, duration in minutes and seconds (walk/cycle), resting and peak heart rate, and any symptoms experienced during exercise. RT records included the amount of weight lifted, and the number of repetitions and sets performed for each workout. This log was submitted and cross validated by a cardiac rehabilitation supervisor at the patient’s weekly visit to the Centre. Patients were trained to measure resting and exercise heart rates at orientation to the program and accuracy was checked at each weekly visit to the Centre.

Walking, stationary recumbent or upright cycling were the modes of AT prescribed depending on individual ability and access to equipment when away from the Centre. Treadmill or overground walking was considered for those who could sustain high enough speeds and
durations to achieve aerobic benefit. Cycle ergometer exercise was prescribed to patients when stroke-related deficits precluded walking. The AT intensity was based on data from the cardiopulmonary exercise test. The goal was to progress patients to 20-60 minutes of exercise (Gordon et al. 2004), 5 times-wk\(^1\) (Hamm and Kavanagh 2000) at an intensity considering a combination of the following: 40-70\% of heart rate reserve or \(\text{VO}_2\text{peak}\) (Gordon et al. 2004), the heart rate achieved at the VAT (Gordon and Scott 1995), and/or a rating of perceived exertion of 11-16 (“light” to “hard”) on the Borg 6-20 Scale (Borg 1982). Prescriptions were initially progressed by increasing duration to ≥20 minutes and then increasing intensity to 70\% of heart rate reserve and/or the heart rate achieved at/above the VAT (maximum duration of 60 minutes). Thereafter, training intensity was adjusted to maintain a heart rate equivalent to 70\% of heart rate reserve and/or that achieved at the VAT on the graded exercise test. Exercise diary information, heart rates measured at the Centre, as well as communication with the patient assisted the case manager in deciding when to increase the prescription.

For RT, the exercises were task specific, incorporating muscle actions that are performed during daily activities. Resistance was provided by hand-held dumbbells, exercise bands (wrist/ankle attachments), or patients’ body weight. A weight load equivalent to 50-60\% of 1 repetition maximum (1RM) was prescribed on the non-affected limb. On the affected limb ≥50\% of 1RM and/or a resistance rated as 13-14 on the Rating of Perceived Exertion scale on the last repetition of the set was prescribed (Marzolini et al. 2008). Patients gradually progressed from 10-15 repetitions and then increased resistance by 1.6-5 kg or increased the exercise band level and then reduced repetitions to 10 and repeated this process.

### 5.3.3 Cognitive Testing

The Montreal Cognitive Assessment (MoCA) was designed as a screening instrument for mild cognitive dysfunction (Nasreddine et al. 2005). The MoCA scores range from 0 to 30 points and has high sensitivity (77\%) and specificity (83\%) for detecting mild cognitive impairment (MCI) in patients in the chronic stage of stroke as determined by a score of <25 (Pendlebury et al. 2012; Pendlebury et al. 2010). However, to ensure that the results were qualitatively similar, a
threshold of <24 was also used, as this threshold has been reported as being the most accurate for predicting MCI in individuals with cardiovascular disease, who are at greater risk of MCI than those in the general population (McLennan et al. 2011). The MoCA assesses 7 different cognitive domains including the following: “visuospatial and executive function” with the adapted Trail Making B task, three-dimensional cube copy, and clock-drawing (5 points); “naming” with confrontation naming (lion, rhinoceros, camel) (3 points); “attention and concentration” including digits forward and backward, vigilance (finger tapping at the letter “A” in a list of letters), and serial subtraction (6 points); “language” including sentence repetition and verbal fluency (3 points); “abstraction” including similarities between two items (2 points); “delayed recall” including short-term memory recall of a list of 5 words (5 points); and “orientation” including date, month, year, day, place and city (6 points). A point was added to the total score for those with 12 or fewer years of education. Koski et al. have shown that the MoCA is a reliable and valid quantitative estimate of cognitive ability and can be used to track changes in cognitive ability over time in a clinical setting (Koski, Xie and Finch 2009). The assessment was conducted in a quiet room without distractions, by two individuals trained in administration of the MoCA questionnaire.

### 5.3.4 Cardiopulmonary Exercise Testing

Medical history and anthropometric measures were collected prior to each cardiopulmonary exercise test. A symptom-limited cardiopulmonary exercise test on a recumbent cycle ergometer with specialized pedals to secure feet (Ergoline Select 1000, Germany) or upright cycle (Ergoselect 200P, Germany), or a treadmill was performed at baseline and after 6 months of training. The type of ergometer was chosen based on balance, and control of leg/foot position in pedals. Work load was increased by either 8.3 or 16.7 Watts every minute. Breath-by-breath gas samples were collected via calibrated metabolic cart (SensorMedics Vmax Encore, California) with continuous monitoring of 12-lead ECG (Marquette Case 8000). Blood pressure was measured at 2 minute intervals. The expected $\text{VO}_{2\text{peak}}$ $(\text{mL-kg}^{-1}\cdot\text{min}^{-1})$ was calculated from
established age and sex norms (Jones and Campbell 1982) for comparison of cardiopulmonary fitness.

Gas Exchange Anaerobic Threshold:

We chose change in oxygen uptake (mL·kg⁻¹·min⁻¹) at the gas exchange anaerobic threshold (VAT) as the independent variable reflecting AT performance rather than peak oxygen uptake (VO₂peak). While improvements in VO₂peak are important for prognostic outcome, delaying the point at which lactate accumulates during exercise has important clinical implications for improving submaximal endurance performance (Marcinik et al. 1991). More importantly, measurement of maximal cardiovascular fitness may be limited by motor and neurological impairments that may prevent individuals from reaching a “true” physiological maximum (Marzolini et al. 'The Feasibility of Cardiopulmonary Exercise Testing for Prescribing Exercise to People after Stroke' 2012) (VO₂max) on the cardiopulmonary exercise test thereby mitigating the utility of VO₂peak measures in correlation analyses.

VAT was determined by a combination of the V-slope method and the ventilatory equivalents methods (Figure 5.1A and B) (Beaver, Wasserman and Whipp 1986; ATS 2003). The V-slope method was defined as the point of departure from linearity of carbon dioxide output plotted against oxygen uptake. The ventilatory equivalent method was defined as the level corresponding to the rise in ventilatory equivalent of oxygen that occurs without a concurrent rise in the ventilatory equivalent of carbon dioxide. The VAT is considered a valid measure demonstrating high reproducibility and low interobserver variability when established standards are followed (Sullivan and Cobb 1990; Meyer et al. 1996). VAT was determined by 2 independent assessors experienced in threshold analysis blinded to the objectives of the study. The final VAT was the average of that obtained by the readers if the values differed by <10%, otherwise they were resolved by consensus. The VAT of both readers were either within 10% of each other or the readers were in concordance that the VAT was indeterminate for 75.6% of the tests at baseline and 80.5% of the tests at 6 months. VAT was discernible at both baseline and 6 months in 68.3% (n=28) patients.
Figure 5.1A and 1B. The Gas Exchange Anaerobic Threshold Determined for One Patient Using the V-slope Method (A) and Ventilatory Equivalents Methods (B)

Gas Exchange Anaerobic Threshold

5.3.5 Body Composition

Total body and regional measurements (arms, legs, and trunk) of fat-free mass, percent body fat, and fat mass were determined by DXA (HOLOGIC QDR 4500 W, Software version 12.3). Pre- and post-study tests were conducted by the same operator. This method of body composition measurement has been shown to have a high level of precision (Mazess, Barden and Bisek 1990).
5.3.6 Muscular Strength

The 1RM test was performed at baseline and following 6 months of training on the bicep curl exercise using hand-held dumbbells and on the leg extension and leg curl exercise on a fixed weight machine on both affected and non-affected limbs as described elsewhere (Marzolini et al. 2008). After 3 repetitions of a warm-up weight, a heavier weight was attempted 1 time following a 2 minute recovery period. One repetition at a heavier weight was attempted every 2 minutes until the patient was unable to lift the weight with proper technique.

5.3.7 Additional Baseline Measures

Baseline assessments included motor recovery stage of the arm, hand, leg and foot of the stroke-affected side classified on the 7 point Chedoke-McMaster Stroke Assessment scale (Gowland et al. 1993). A Chedoke-McMaster Stroke Assessment scale motor impairment score of 1 indicates flaccid paralysis, 3 describes marked spasticity and weakness, 6 indicates near normal coordination of patterns of movement and no spasticity, and 7 describes normal movement (Gowland et al. 1993). Depressive symptoms were assessed using the CES-D scale with scores $\geq 16$ demonstrating high sensitivity and specificity for detecting depression (Radloff 1977) and is a valid and reliable measure for the stroke population (Shinar et al. 1986). Six minute walk distance (6MWD), as described elsewhere (ATS 2002) was conducted pre- and post-program.

5.3.8 Statistics

Data are presented as means ± SD unless otherwise indicated. Baseline and post-exercise scores were compared using Student’s $t$-tests for paired samples. A chi square test was used to compare categorical variables. Five cases were removed from the “time from stroke” data for correlation analyses as they were $\geq 3$ standard deviations above the mean (650-135 weeks following stroke to commencement of program). The relationship between change in cognition scores and change in VAT and fat-free mass were determined using the Pearson correlation coefficient. A linear regression model was fitted, regressing domains of change in cognition with VAT and fat-free mass controlling for sex, age, time from stroke, change in fat mass, and
baseline and change in CES-D score. We selected a final model forcing VAT or fat-free mass into the respective model and selecting variables into the model if it changed the crude VAT or fat-free mass parameter estimate more than 15%. Probability values <0.05 were considered significant. All analyses were performed in SPSS (version 19.0, SPSS, Inc., Chicago, IL).

5.4 Results

Of the 45 patients who agreed to participate in the study, 91% (n=41) completed 6 months of exercise training. Reasons for discontinuing the program were owing to re-occurrence of cancer (n=1), transportation difficulties (n=1), re-occurrence of stroke (3rd stroke) unrelated to exercise (n=1), death of spouse (n=1). Subject characteristics are presented in Table 5.1. Completers were a mean of 63.6±13.5 years of age, and 74±134.5 weeks (range 10-650) post-stroke with the majority being >6 months post-stroke (80.5%). Most patients were male (73.2%), post-ischemic stroke (65.9%), using an assistive device for ambulation (75.6%) with mild cognitive impairment (65.9%). At baseline, 22.5% of patients had depressive symptoms. Patients attended 83.5±16% of weekly classes, and completed 70±37.5% of prescribed AT and 80.4±46.4% of prescribed RT sessions. While each RT program was individualized, the forward lunge, standing squat, and bicep curl exercises were common to most patients. Mean AT distance, time, intensity, and heart rate, as well as the RT weight load lifted ascertained by diary and cross-validated by in-class performance increased significantly (Table 5.3). There were no associations between the change in cognitive outcomes and either accomplished work over time or change in 6MWD.

Following 6 months of AT+RT there were significant improvements in $\dot{V}O_{2\text{peak}}$ (p<0.001), oxygen uptake at the VAT (p=0.006), non-affected arm fat-free mass (p=0.01), upper and lower limb muscular strength (1RM) (all, p<0.007), and 6MWD (p<0.001). There was no significant change in depression score (Table 5.2). The proportion of people who scored <25 on the MoCA (threshold criteria for MCI in chronic stroke), decreased from 65.9% (n=27) to 36.6% (n=15), p<0.001 (Table 5.4). The proportion of people who scored <24 on the MoCA (threshold criteria for MCI in cardiovascular disease), decreased from 51.2% (n=21) to 34.1% (n=14), p<0.001. None of the patients developed MCI de novo at 6 months. There were significant improvements
in overall MoCA score as well as in the subdomains of visuospatial/executive function, and attention/concentration.

There was a significant positive association between change in total cognition score and both change in fat-free mass of the non-affected limbs (β=0.002, p=0.005) and change in total appendicular (all limbs) fat-free mass (β =0.001, p=0.02) independent of age, sex, time from stroke, change in fat mass and baseline or change in depression score. However, change in fat-free mass of the non-affected limbs accounted for a greater proportion of the variance in change in cognition score (16%) than did change in appendicular fat-free mass (11.9%). There was a significant positive association between change in attention/concentration and change in the oxygen uptake at the VAT mL·kg⁻¹·min⁻¹ (β=0.383, p=<0.001), independent of age, sex, time from stroke, change in fat mass and baseline or change in depression score. Change in VAT accounted for 40.9% of the variance in change in attention/concentration score.

There were no differences in any of the cognitive outcomes when analyzed by sex, medications (aspirin, statins, beta-blocker, antidepressant), type of stroke (hemorrhagic vs. ischemic), education, history of depression requiring medication, depression score, or comorbid diagnoses (p>0.05 for all). There were no significant correlation between “time from stroke” and change in cognitive measures with the exception of the subdomain of “naming” (r= -0.4, p=0.02) (Table 5.3).
Table 5.1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=41</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>30 (73.2)</td>
</tr>
<tr>
<td>Age, years (range)</td>
<td>63.6±13.5 (27-88)</td>
</tr>
<tr>
<td>Partnered, n (%)</td>
<td>35 (85.4)</td>
</tr>
<tr>
<td>Education, ≥13 years, n (%)</td>
<td>29 (70.7)</td>
</tr>
<tr>
<td>Time post-stroke, weeks (range)</td>
<td>74.0±135 (10-650)</td>
</tr>
<tr>
<td>Body Mass, kg</td>
<td>77.9±15.8</td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>26.7±4</td>
</tr>
<tr>
<td>Obesity, body mass index ≥30, n (%)</td>
<td>10 (24.4)</td>
</tr>
<tr>
<td>Waist Circumference, cm</td>
<td>96.9±12.1</td>
</tr>
<tr>
<td>Waist to Hip Ratio</td>
<td>0.95±0.06</td>
</tr>
<tr>
<td>% Body Fat</td>
<td>28.7±6.0</td>
</tr>
<tr>
<td>Ischemic/Hemorrhagic/Unknown Stroke Type, n (%)</td>
<td>27(65.9)/13(31.7)/1(2.4)</td>
</tr>
<tr>
<td>Right/Left Hemisphere Affected, n (%)</td>
<td>20(48.8)/21(51.2)</td>
</tr>
<tr>
<td>Coronary Artery Disease n (%)</td>
<td>8 (19.5)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>12 (29.3)</td>
</tr>
<tr>
<td>Atrial Fibrillation, n (%)</td>
<td>8 (19.5)</td>
</tr>
<tr>
<td>History of Depression Requiring Medication, n (%)</td>
<td>9 (22)</td>
</tr>
<tr>
<td>Past Smoker, n (%)</td>
<td>15 (36.6)</td>
</tr>
<tr>
<td>Current Smoker, n (%)</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>Alcohol, n (%)</td>
<td>11 (26.8)</td>
</tr>
<tr>
<td>Gait aids, None/Cane/Rollator, n (%)</td>
<td>10(24.4)/20(48.8)/11(26.8)</td>
</tr>
<tr>
<td>Chedoke-McMaster Stroke Assessment Scores</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Arm</td>
<td>4.2±1.7 (1-7)</td>
</tr>
<tr>
<td>Hand</td>
<td>4.2±2.0 (1-7)</td>
</tr>
<tr>
<td>Leg</td>
<td>4.9±1.0 (3-6)</td>
</tr>
<tr>
<td>Foot</td>
<td>4.1±1.7 (1-7)</td>
</tr>
<tr>
<td>Resting Systolic Blood Pressure</td>
<td>124.1±15.5</td>
</tr>
<tr>
<td>Resting Diastolic Blood Pressure</td>
<td>76.7±9.7</td>
</tr>
<tr>
<td>Medications, n (%)</td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>13 (31.7)</td>
</tr>
<tr>
<td>Ca²⁺-channel antagonists</td>
<td>11 (26.8)</td>
</tr>
<tr>
<td>Other Antihypertensives</td>
<td>25 (61)</td>
</tr>
<tr>
<td>Lipid lowering agents, Statins</td>
<td>29 (70.7)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>16 (39)</td>
</tr>
<tr>
<td>Antidiabetic agents</td>
<td>9 (22)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>7 (17.1)</td>
</tr>
<tr>
<td>Antianxiolytics</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>3(7.3)</td>
</tr>
<tr>
<td>Attendance, % of weekly sessions</td>
<td>83.5±16</td>
</tr>
<tr>
<td>Mean AT frequency per week, n (% of prescribed sessions)</td>
<td>3.5±1.9 (70.0±37.5%)</td>
</tr>
<tr>
<td>Mean RT frequency per week, n (% of prescribed sessions)</td>
<td>1.6±0.9 (80.4±46.4%)</td>
</tr>
<tr>
<td>RT Exercises Prescribed, n (range)</td>
<td>10.9±2 (8-14)</td>
</tr>
<tr>
<td>RT Exercises Prescribed (Lower/Upper Body/Trunk-stabilizing), %</td>
<td>62.4±10.6/26.2±10.6/10.9±4.1</td>
</tr>
<tr>
<td>Resistance (Dumbbells/Elastic Bands/Body Mass), %</td>
<td>24.3±11.8/29.4±11.4/46.2±12.8</td>
</tr>
</tbody>
</table>

All data are presented as mean ± SD unless otherwise indicated.

AT=Aerobic training
RT=Resistance training
Table 5.2. Change in Physiological and Depression Measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>6 Months</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Mass</td>
<td>78.5±15.9</td>
<td>78.5±15.0</td>
<td>0.96</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>26.7±4.0</td>
<td>26.8±3.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Peak Oxygen Uptake (mL·kg⁻¹·min⁻¹)</td>
<td>15.3±4.9</td>
<td>17.9±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age and Gender Predicted Norms, %</td>
<td>66.2±24.2</td>
<td>78.4±30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory Exchange Ratio</td>
<td>1.1±0.2</td>
<td>1.1±0.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Peak HR Achieved</td>
<td>108.9±22.6</td>
<td>116.3±24.9</td>
<td>0.006</td>
</tr>
<tr>
<td>Peak Workload, Watts</td>
<td>63.0±24.5</td>
<td>78.1±36.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Oxygen Uptake at the VAT (mL·kg⁻¹·min⁻¹)</td>
<td>13.4±4.2</td>
<td>14.7±4.2</td>
<td>0.006</td>
</tr>
<tr>
<td>Six Minute Walk Distance, metres</td>
<td>274.9±115.7</td>
<td>331.0±130.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Body FFM, kg</td>
<td>52.4±11.4</td>
<td>52.6±10.9</td>
<td>0.7</td>
</tr>
<tr>
<td>% of Total Body Mass</td>
<td>67.8±5.4</td>
<td>68.0±5.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Appendicular FFM, kg</td>
<td>21.9±5.0</td>
<td>22.1±4.9</td>
<td>0.3</td>
</tr>
<tr>
<td>FFM Non Affected Limbs, kg</td>
<td>11.4±2.7</td>
<td>11.5±2.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Arm FFM Non affected, kg</td>
<td>2.84±0.75</td>
<td>2.91±0.78</td>
<td>0.01</td>
</tr>
<tr>
<td>Leg FFM Non affected, kg</td>
<td>8.57±1.94</td>
<td>8.59±1.88</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Affected Limbs, kg</td>
<td>Control Limbs, kg</td>
<td>p</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------------------</td>
<td>-------------------</td>
<td>-------</td>
</tr>
<tr>
<td>FFM</td>
<td>10.53±2.4</td>
<td>10.6±2.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Arm FFM</td>
<td>2.477±0.63</td>
<td>2.53±0.67</td>
<td>0.06</td>
</tr>
<tr>
<td>Leg FFM</td>
<td>8.05±1.9</td>
<td>8.04±1.8</td>
<td>0.9</td>
</tr>
<tr>
<td>1 RM Affected Bicep Curl, kg</td>
<td>4.5±3.9</td>
<td>5.7±4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>as % Body Mass, n=39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 RM Non Affected Bicep Curl</td>
<td>12.4±4.1</td>
<td>13.7±4.1</td>
<td>0.006</td>
</tr>
<tr>
<td>as % Body Mass</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 RM Affected Leg Extension,</td>
<td>27.9±15.8</td>
<td>35.3±19.5</td>
<td>0.002</td>
</tr>
<tr>
<td>kg as % Body Mass, n=37</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 RM Non Affected Leg</td>
<td>52.0±18.6</td>
<td>60.1±17.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Extension, kg as % Body Mass</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CES-D score</td>
<td>9.3±8.2</td>
<td>10.4±8.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

VAT=Gas exchange anaerobic threshold
FFM=fat-free mass
1RM=one repetition maximum
CES-D= Center for Epidemiologic Studies Depression
## Table 5.3. Exercise Performance at Baseline and Following 6 months of Training

<table>
<thead>
<tr>
<th>Exercise Characteristic</th>
<th>Baseline</th>
<th>Final</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walk Distance, km n=34</td>
<td>0.97 ± .84</td>
<td>1.8 ± 1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Time, Minutes</td>
<td>18.2 ± 9.8</td>
<td>29.6 ± 11.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pace, km/hour</td>
<td>2.9 ± 1.2</td>
<td>3.3 ± 1.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Cycle, Total Time, Minutes n=12</td>
<td>15.2±7.7</td>
<td>21.7±8.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Exercise Time, Cycle Only, Walk Only, or Walk and Cycle Combination, Minutes</td>
<td>20.6±9.7</td>
<td>32.0±11.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exercise HR, BPM (range)</td>
<td>89.1±15.8 (60-119)</td>
<td>99.1±18.9 (60-132)</td>
<td>0.01</td>
</tr>
<tr>
<td>Exercise HR, % of peak HR from baseline test (range)</td>
<td>79.9±12.1 (54-99)</td>
<td>90.9±15.2 (61.9-140)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bicep Curl kg, Affected Arm, kg (n=35)</td>
<td>2.3±1.5</td>
<td>3.6±2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% of Baseline 1 RM</td>
<td>64.4±38.2</td>
<td>112.3±83.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bicep Curl, Non Affected Arm, kg</td>
<td>4.9±3.3</td>
<td>6.4±3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% of Baseline 1 RM</td>
<td>49.9±19.1</td>
<td>66.8±21</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BPM=beats per minute
HR=heart rate
1RM= one repetition maximum
Table 5.4. Change in Cognitive Measures and Correlation with Time from Stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>6 Months</th>
<th>P Value</th>
<th>Correlation between Change Score and Time from Stroke (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoCA score</td>
<td>22.5±4.5 (12-30)</td>
<td>24.0±3.9 (16-30)</td>
<td>&lt;0.001</td>
<td>0.07 (0.7)</td>
</tr>
<tr>
<td>Mild Cognitive Impairment</td>
<td>27 (65.9)</td>
<td>15 (36.6)</td>
<td>&lt;0.001</td>
<td>------</td>
</tr>
<tr>
<td>(MoCA score&lt;25), n %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visuospatial/executive</td>
<td>3.4±1.1 (0-5)</td>
<td>3.9±1.1 (1-5)</td>
<td>0.002</td>
<td>0.2 (0.4)</td>
</tr>
<tr>
<td>Attention/concentration</td>
<td>4.7±1.7 (0-6)</td>
<td>5.2±1.3 (1-6)</td>
<td>0.03</td>
<td>-0.04 (0.8)</td>
</tr>
<tr>
<td>Naming</td>
<td>2.8±0.5 (1-3)</td>
<td>2.9±0.5 (1-3)</td>
<td>0.4</td>
<td>-0.4 (0.02)</td>
</tr>
<tr>
<td>Language</td>
<td>1.3±1.1 (0-3)</td>
<td>1.4±1.0 (0-3)</td>
<td>0.4</td>
<td>0.2 (0.3)</td>
</tr>
<tr>
<td>Abstraction</td>
<td>1.7±0.6 (0-2)</td>
<td>1.6±0.7 (0-2)</td>
<td>0.3</td>
<td>-0.1 (0.6)</td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>2.8±1.8 (0-5)</td>
<td>3.0±1.9 (0-5)</td>
<td>0.4</td>
<td>0.07 (0.7)</td>
</tr>
<tr>
<td>Orientation</td>
<td>5.6±0.9 (2-6)</td>
<td>5.8±0.4 (5-6)</td>
<td>0.1</td>
<td>-0.4 (0.9)</td>
</tr>
</tbody>
</table>

MoCA=Montreal Cognitive Assessment

5.5 Discussion

In patients with residual motor impairment post-stroke, a 6 month combined AT+RT exercise program resulted in significantly improved MoCA scores, and a drop of nearly half (44.5%) in the proportion of patients meeting threshold criteria for MCI. Improvement was characterized by gains in the sub-domains of attention/concentration and visuospatial/executive functioning. These results are consistent with those from healthy, sedentary adult populations, in which AT and RT in combination resulted in significantly greater improvements in cognitive function than AT alone (Colcombe and Dramer 2003). Previously, one study examining the effects of combined AT+RT exercise on cognition post-stroke, reported significant improvement in
working memory, a component of executive function, in 9 patients after 12 weeks of training (Kluding, Tseng and Billinger 2011). In contrast, a pilot study randomizing 19 individuals post-stroke to 8 weeks of AT alone, resulted in greater improvements in motor learning, but not executive function compared to those (n=19) randomized to the control group (Quaney et al. 2009) suggesting that the addition of RT may be associated particularly with cognitive advantage.

While the addition of RT to AT may offer incremental benefit, possible mediators of this relationship have not been studied extensively. In the present study, cognitive improvement was independently associated with fat-free mass accretion of non-affected limbs. This finding is consistent with recent cross-sectional studies linking poorer cognitive performance with reduced fat-free mass. For instance, Nourhashemi et al. reported that women in the lowest quartile of fat-free mass, as measured by DXA, had an odds ratio of 1.43 for cognitive impairment compared with those in the highest quartile of fat-free mass after adjusting for confounders (Nourhashemi et al. 2002). Burns et al. evaluated 70 individuals with early-stage Alzheimer disease and 70 individuals without dementia, using brain magnetic resonance imaging, neuropsychological testing, and DXA scans (Burns et al. 2010). They found that there was a positive association between fat-free mass and whole brain volume in both groups. There was also a significant correlation between fat-free mass and global cognitive performance. While these studies do not infer causation, an anabolic stimulus may enhance cognitive performance and, based on our findings, RT is feasible, and potentially of clinical utility in patients post-stroke. These findings strongly suggest the need for larger randomized trials.

Compared to fat-free mass accretion, cardiopulmonary fitness has been more extensively studied as a possible contributor to cognitive performance (Swardfager et al. 2010). For instance, Kluding et al., reported a correlation between improved \( \dot{V}O_2^{\text{peak}} \) and improved executive control on the Flanker test in individuals post-stroke participating in AT+RT (Kluding, Tseng and Billinger 2011). However, an earlier meta-analysis and a systematic review of 10 and 11 studies respectively, did not substantiate an association between changes in \( \dot{V}O_2^{\text{peak}} \) and changes in cognitive function (Angevaren et al. 2008; Etnier et al. 2006). The association we observed between change in attention/concentration and change in oxygen uptake at the VAT extends
these findings. In clinical populations, factors that limit individuals in reaching $\dot{V}O_{2\text{max}}$ on an exercise stress test such as lack of motivation, depressive symptoms (Lavoie et al. 2004), musculoskeletal issues, and neurological deficits may reduce the utility of the $\dot{V}O_{2\text{peak}}$ as a measure of cardiopulmonary fitness. More easily attained submaximal measures of oxygen uptake, specifically that occurring at the VAT, might provide a more reliable measure; in a previous study of 98 individuals post-stroke, 67% reached VAT whereas only 18% achieved $\dot{V}O_{2\text{max}}$ (Marzolini et al. 'The Feasibility of Cardiopulmonary Exercise Testing for Prescribing Exercise to People after Stroke' 2012). VAT indicates the VO$_2$ at which anaerobic energy production mechanisms contribute to the oxidative energy system (ATS 2003), with concomitant increases in ventilation and peripheral lactate concentrations (Wasserman et al. 1973). Since cerebral lactate uptake is proportional to peripheral arterial concentrations (Rasmussen, Wyss and Lundby 2011), the VAT might provide a more metabolically relevant measure than the $\dot{V}O_{2\text{peak}}$ that also reflects cerebral metabolism. With a training-induced increase in oxygen uptake at the VAT, persons who are living with the effects of a stroke are more likely to perform daily activities at a level where cerebral energy metabolism is predominantly aerobic. These possible implications require further investigation.

It is reported that patients with cognitive impairment following stroke will exhibit deficits in attention, executive function, and processing speed related to frontal network dysfunction (Tatemichi et al. 1994). Moreover, in healthy individuals, it is reported that the cognitive subdomains of attention and executive processes are the ones that will benefit most from an exercise intervention (Colcombe and Dramer 2003). This may explain in part why there were significant improvements in the subdomains of attention/concentration and executive function and not in other subdomains in the current study.

Collectively, there is compelling evidence that a combined training approach (AT+RT) enhances cognition post-stroke. Our findings indicate that accretion of muscle has the potential for cognitive gain. While training of the affected limb is important and often the focus of treatment, RT of the non-affected side should not be neglected. Given the link between improved oxygen uptake at the VAT and gains in cognition, exercise prescription methods should be based on
results of a cardiopulmonary exercise test to ensure an exercise intensity that provides adequate cardiovascular stress to induce a training response.

### 5.6 Limitations

A limitation of this study was the relatively small sample size of non-randomly selected individuals following stroke and the multiple comparisons made. A further limitation was the use of a single neurocognitive measure and the pre- post-test design. To elucidate a cause and effect relationship between exercise and change in cognitive function, a randomized controlled study is required. However, the independent correlation between change in physiological measures and cognitive change support an effect of the intervention.

Although we did not have a comparison control group, the relative magnitude of the physiological change suggests that both the AT and RT interventions were effective. We observed a mean increase in \( \dot{V}O_{2\text{peak}} \) (mL·kg\(^{-1}\)·min\(^{-1}\)) of 18.8±24.4% which is greater than the 10.7% to 13.2% improvement reported in 3 studies (Lennon et al. 2008; Potempa et al. 1995; Pang et al. 2005) and 17% gain reported in 1 study (Macko et al. 2005) in chronic stroke patients randomized to an exercise intervention; changes that were significantly greater than control groups. Moreover, the relative magnitude of change in the present study is similar to that reported in cardiac patients (9-18%) participating in exercise programs tested at the same centre (Marzolini et al. 2008; Marzolini, Candelaria and Oh 2010) and elsewhere (Milani, Lavie and Mehra 2004; Lavie and Milani 200). In addition, the 10.8±18.6% change in the VAT in the present study was similar to relative gains experienced by cardiac patients following an exercise program; 4 studies yielded changes ranging from 2-11% (Milani, Lavie and Mehra 2004; Marzolini et al. 2008; Carlson et al. 2000; Lavie and Milani 200) and 1 study reported a 15.2% (Pierson, Herbert and Norton 2001) change. Also, exercise training yielded a gain of 56.1±47.1 metres in functional exercise capacity measured by the 6MWD test and was similar to the change reported by others (49.1-64.6 metres) (Macko et al. 2005; Pang et al. 2005) that were significantly greater than control patients with chronic stroke.
The significant improvement in muscular strength for upper and lower body affected and non-affected limbs suggests effective RT. However, while, there was no significant increase in overall fat-free mass as measured by DXA, regional measures showed a significant change in non-affected arm fat-free mass and trend for change in the affected arm. Similarly, Ryan et al. (Ryan et al. 2011) showed no change in overall fat-free mass measured by DXA as a result of an RT program in people following chronic stroke. However, the investigators reported a significant increase in paretic and non-paretic muscle area of the mid-thigh as measured by multi-slice CT scanning. This suggests that CT scanning may provide a more effective measure of change in fat-free mass in stroke patients. DXA-prediction models have been reported to overestimate total body skeletal muscle by the amount of intra-and inter-muscular fat present, that may not be considered in the prediction model (Kim et al. 2004). Ryan and colleagues demonstrated significantly greater intramuscular fat deposits in paretic compared to non-paretic thigh muscle (Ryan et al. 2002) and that RT resulted in reductions in intramuscular fat in both mid thighs following stroke (Ryan et al. 2011). Thus an accurate measure of intramuscular fat in the larger muscle groups would be important for detecting change in fat-free mass in this population and may explain in part, the lack of change in overall fat-free mass measured by DXA in the larger muscle groups.

Further, the lack of effect that stroke recovery time to initiation of the program had on change in overall cognition in this study suggests spontaneous recovery played an inconsequential role on outcomes. Moreover, more than 80% of the patients started cardiac rehabilitation more than 6 months post-stroke, and while there does not appear to be a consensus, previous research trends towards an indication that unappreciable changes in cognition occur after the first 3 to 6 months of recovery (Kelly-Hayes et al. 1989; Pederson et al. 1995; Cassidy, Lewis and Gray 1998). In view of the mixed facility and home-program treatment model, the added attention and interaction from the single on-site 90 minute weekly appointment is unlikely to have a significant effect on cognition. Rather, subjects would likely have experienced less social contact than received from the 3 times weekly traditional stroke rehabilitation visits that many would have completed in the first 3-4 months post-stroke. Also, owing to the heterogeneity of mobility function, minimal between-patient interaction occurred during stationary cycling or walking on the 200 meter track during the supervised sessions.
The sample of 41 subjects and exclusion of patients who were not able to walk ≥10 meters with/without a gait aid limits the generalizability of this study. However, the physical profile is consistent with other studies, and the high prevalence of mild cognitive deficits is consistent with that previously reported in the stroke population (Ya-Ping et al. 2006). Nutrition status was not assessed and may have had an effect on body composition. Finally, while we did not formally assess inter-tester reliability of the MoCA, the training of the 2 administrators of the MoCA was conducted by a psychologist, and informal “calibration” meetings were conducted when a score required verification.

5.7 Conclusions

A cardiac rehabilitation model of AT+RT result in improvements in overall cognition and in the subdomains of attention/concentration and visuospatial/executive function. There was a 44.5% reduction in the proportion of patients meeting the threshold criteria for MCI. Change in cognition was associated with change in the gas exchange anaerobic threshold, and fat-free mass of the non-affected limbs; indices typically attributed to AT and RT respectively.

5.8 Acknowledgements

We acknowledge the contribution of Susie Ward, Dr. Gail Kunkel, Brandon Zagorski, Daryl Dooks, Dr. Don Mertens, and patients and staff at Toronto Rehab.
Chapter 6 GENERAL DISCUSSION

Building on previous research conducted by others (Lennon et al. 2008; Tang et al. 2010), we have presented novel data supporting the feasibility and effectiveness of components of CR interventions and assessments in individuals post-stroke. In Chapter 2, we demonstrated the utility and feasibility of the CPET for prescribing safe and efficacious exercise in people with motor impairments following stroke. Particularly striking was the significant rate of clinically relevant abnormalities uncovered during these assessments and the mitigated utility of the CPET for women at baseline. While these results demonstrate the importance of conducting CPETs, they also uncover gender differences unique from the CAD population that require further investigation. Yet, establishing appropriate target exercise levels through CPET assessments would be inconsequential if people with neurologic impairments were not able to systematically meet the minimal exercise target levels during a typical exercise session. Thus, in Chapter 3 we demonstrated that people following stroke were able to meet or exceed minimal intensity, duration and energy expenditure target levels during 30 minutes of AT combined with 30 minutes of RT after completing a CR program. Noteworthy was the contribution of RT to the cardiovascular stimulus, suggesting RT may serve as an important exercise modality that may be of particular benefit to those unable to ambulate at intensities sufficient to elicit aerobic benefit.

The results of the studies examining the acute effects of exercise presented in Chapters 2 and 3 would be of little importance if the established exercise training program did not result in favorable outcomes to the individual. Consequently, in Chapters 4 and 5 we demonstrated that the beneficial effects of a 6 month CR program with AT and RT as corner stone therapies, extended beyond the improvement in cardiovascular fitness. Specifically, there were post-program gains in ambulatory function, muscular strength, sit-to-stand performance and cognitive function. Moreover, individuals referred to CR both in the early chronic phase of stroke (≤1 year post-stroke) and late chronic phase (>1 year) demonstrated benefits. The ongoing improvement in these parameters of recovery after individuals had received all of the TSR available to them, suggests that treatment should not terminate when an early recovery plateau is reached with conventional treatments offered in TSR. The plateau may in fact be part of an ongoing adaptive
pattern (Page, Gater and Bach-y-Rita 2004) that would allow individuals to reach higher levels of function if a different treatment were introduced such as the AT and RT components of a CR program. Contrary to our hypothesis that change in ambulatory function would be independent of time from stroke to commencement of the exercise program, CR participation early in the chronic phase of stroke (≤1 year post-stroke) yielded greater advantage for ambulatory function (6 minute walk distance, 5 metre fast paced walking speed, and non-paretic step length) compared to participation later after stroke (>1 year). These findings will help to encourage practitioners to adopt a seamless referral process to CR programs following TSR.

In Chapter 5 we demonstrated that a 6 month program of AT and RT resulted in significant improvements in cognitive function score that was positively associated with change in VAT and muscle mass accretion independent of age, sex, time from stroke, fat mass, and baseline and change in depressive symptoms. Identification of muscle mass accretion and change in VAT as potential mediators of cognitive change suggests that an RT exercise program, with its anabolic component can ameliorate cognitive deficits and that these effects may be intensified when combined with AT. Also, the association between an increase in VAT and gains in cognition suggest that exercise prescription methods should be based on results of a CPET to ensure an exercise intensity that provides adequate cardiovascular stress to induce a training response. These results strongly suggest a need for randomized controlled trials to elucidate the mediators of cognitive change and to determine treatment strategies to improve brain health in people recovering from stroke.

**Cardiopulmonary Exercise Stress Testing for People Following Stroke**

The rate of clinically relevant abnormalities from CPETs (Chapter 2) warrants further discussion. We reported that more than 1 in 10 patients following stroke developed a significant abnormality that would prohibit exercise beyond the intensity where it occurred due to increased risk of an acute cardiac event or elevated mortality risk. In addition, these abnormalities occurred equally in those with and without coexisting CAD. Moreover, rate of clinically relevant abnormalities were equal to that of patients in the CAD cohort at both time points despite reaching a significantly lower CPET intensity. Over half of the clinically relevant abnormalities that
occurred on the CPET in the stroke cohort were attributed to complex ventricular ectopy both at baseline and follow-up assessments. The clinical significance of this is unclear. A study of 6,000 asymptomatic men followed for 23 years, showed that exercise-induced ventricular ectopy was associated with a relative risk of death from cardiovascular disease of approximately 3.0 (Jouven et al. 2000). In a larger study, 29,444 individuals referred for exercise stress testing without valve disease or history of heart failure were followed for a mean of 5.4 years (Frolkis et al. 2003). Frequent ventricular ectopy (≥7 VPB’s per minute) during exercise and in recovery predicted an increased risk of death (OR 2.4; 95CI, 2.0-2.9; p<0.001). Finally, in a large U.S. community-based cohort, 14,783 men and women were followed for 15 years. Presence of ventricular ectopy at baseline was associated with increased incidence of stroke. The unadjusted hazard ratio of stroke in individuals with any ventricular ectopy compared with those without any ventricular ectopy was 1.71 (95% CI, 1.3 to 2.20) (Agarwal et al. 2010).

The presence of complex ventricular ectopy may be related to underlying ischemia or an increased propensity for arrhythmias through non-ischemic related pathways (Carrim and Khan 2005; Myerburg 1987). In the acute stage of stroke, complex ventricular ectopy is common and has been associated with electrical instability, elevated catecholamine levels, and sympathetic hyperactivity from acute cerebral events (Mikolich, Jacobs and Fletcher 1981). However, the individuals included in the present study were at least 3 months post-stroke and these mechanisms were unlikely to apply. Regardless of the underlying mechanism, the presence of frequent ventricular ectopy is associated with impaired ventricular filling and have the potential for remodeling of the heart (Takemoto et al. 2005; Sun et al. 2003). Collectively, these studies suggest that identification of the exercise intensity level coinciding with the onset of complex high grade ventricular arrhythmias through CPET assessment may prevent exercise above the ischemic or pro-arrhythmic thresholds and may in the long-term help prevent adverse outcomes.

Sex Differences

Several sex differences were revealed in the study presented in Chapter 2 examining utility of the CPET for exercise prescription. First, among the sample of consecutively enrolled patients referred to CR, a significantly smaller proportion of participants were women (30% of all
referrals). Yet, the lifetime incidence of stroke after the age of 55 has been reported to be higher in women than men (1 in 5 women vs. 1 in 6 men) (Seshadri et al. 2006) and in the United States, 60,000 more women than men have a stroke each year (Rosamond et al. 2008). These population data suggest that the proportion of referrals to CR should be at least the same, if not greater for women than men. Reasons for sex difference in referral patterns are often multifactorial as demonstrated in the CR literature (Grace et al. 2002; Daly et al. 2002) and our results strongly suggest the need for focused exploration of barriers to participation in this population. An argument could be made that CR participation may be critical given that pre-stroke and post-stroke disability and rates of institutionalization are significantly higher in women than men (Petrea et al. 2009). Certainly, we showed that at entry to CR, women had a significantly lower functional capacity than men measured by CPET (age- and sex-normative values) but after a program of AT and RT, gains in cardiovascular fitness on the 6 month test placed women at a similar cardiovascular fitness level to both men following stroke, and to women with CAD. Moreover, large prospective cohort studies also support the benefit of physical activity for women. The Women’s Health Study followed 39,315 women for a mean of 11.9 years and demonstrated that there was an inverse association of borderline significance between leisure-time physical activity and risk of stroke (Sattelmair et al. 2010). There was a 17% reduction in stroke risk for the most active compared to the least active women. Also, a meta-analysis of 33 prospective cohort and 10 case control studies revealed that physical activity was associated with a 24% reduction in risk of ischemic stroke in women and 27% reduction in men, however the results for women did not reach significance (Reimers, Knapp and Reimers 2009). While the evidence supporting the benefit of regular physical activity for prevention of stroke is not as strong for women as it is for men, this is possibly related to that lack of studies that have included women. Nevertheless, exploration of the sex difference in referral to secondary prevention and exercise programs merits investigation so that barriers can be removed, providing equal access to care following TSR.

One of the barriers to referral may be related to baseline demographics, specifically participant age at the time of the referral. The women referred to CR following stroke were of similar age as the men referred to CR (62.7 vs. 63.6 years respectively, not significant). Yet, at the time of first ever stroke women are significantly older than men (75.1 vs. 71.1 years respectively, p<0.001)
with a higher incidence of stroke after the age of 85 years, and lower in younger age categories (Petrea et al. 2009). Therefore, women referred to CR were more than 10 years younger than the mean age at time of first ever stroke in the population. This finding suggests a bias towards younger women being referred to CR. Because younger women may have less disability and greater functional capacity, the entry criteria to the CR program (i.e. ability to walk at least 10 meters with or without a gait aide) may have contributed to the younger age of women at entry to CR. Moreover, the lower average age of referral to the adapted CR program following stroke for both men and women compared to the average age at index stroke event suggests that younger men and women are preferentially referred to CR with a particular bias towards referring younger women.

**Effects of Time Elapsed from Stroke Event to Commencement of Cardiac Rehabilitation**

The results from Chapter 4 demonstrating greater gain in ambulatory function, walking speed and non paretic side step length in the earlier entry group (≤1 year post-stroke) compared to the later entry group (>1 year post-stroke) requires further discussion. Elucidating the underlying mechanisms responsible for these findings would aid in selecting treatment strategies for improving physiological outcomes post-stroke.

The underlying mechanisms for the greater change in walking speed during the 5 meter and 6 minute walk distance in the earlier entry compared to later entry group are likely multi factorial. In a study conducted by Patterson et al., it was reported that two-thirds of the change in gait speed in people in the chronic stage of stroke was related to change in stride length (bilateral step length) while one-third was related to change in cadence (Patterson et al. 2008). The earlier entry group of the current study demonstrated both a significant increase in bilateral step length and cadence while the later entry group demonstrated only a significant increase in cadence. Therefore, reliance on increased cadence to augment gait speed by the later entry group was likely associated with a less favorable change. Also, only the earlier entry group demonstrated a significant increase in affected-side hip range of motion. It is likely that greater ability to flex at the hip, especially on the affected side, may play a role in augmenting gait speed possibly by facilitating a longer affected side step length; a change that was observed only in the earlier entry
group. Nevertheless, behavioral compensation strategies and spontaneous recovery can not be ruled out as factors contributing to the more favorable change in gait speed in the earlier entry group.

Greater baseline and post-training paretic side leg strength may have also been a factor that contributed to the superior change in ambulatory performance in the earlier entry compared to the later entry group. Paretic-side leg muscle strength has been reported to be a stronger predictor of gait performance than non-paretic-side leg strength, explaining up to 50% of the variance in gait performance (Flansbjer, Downham and Lexell 2006; Hsu, Tang and Jan 2003). While paretic-side leg strength improved both for the earlier and later entry groups, strength remained significantly lower in the later entry group post-training and may have mitigated their ability to improve ambulatory performance. The correlates of walking speed in people following stroke have been reported to differ between long and short distances and between those with mild and severe hemiparetic gait deficits (Patterson et al. 2007) suggesting a complex series of factors that may account for the differences observed in the present study between earlier and later entry groups that require further investigation.

Another plausible mechanism for the superior change in ambulatory function in the early entry group that requires further investigation may be related to a diminished ability for subcortical reactivation as the amount of time from stroke increases. Although both groups were outside of the optimal window of time when the brain is reported to be most responsive to change (i.e. within 3 months of the stroke event) (Biernaskie, Chernenko and Corbett 2004; Ottenbacher and Jannell 1993; Kwakkel, Kollen and Twisk 2006), recent evidence suggests that these changes are possible in the chronic stage of stroke recovery. For example, Luft et al. showed that 6 months of treadmill exercise in patients >6 months post-stroke resulted in greater affected brain activation measured by functional magnetic resonance imaging during paretic but not during non-paretic limb movement in the cerebellum and midbrain which did not occur in a non-exercise control group (Luft et al. 2008). Notably, increased brain activation correlated with improved walking velocity in the exercise group. This relationship between brain activation and change in walking velocity suggests that the greater change in ambulation in the earlier entry
group of the current study may in part be related to greater neural network plasticity which may play a diminishing role as stroke recovery time increases. This would require further investigation.

Baseline measures revealed longer step length on the paretic compared to the non-paretic limb, and while variability has been demonstrated in step length asymmetry, some investigators have reported this as a common deviation in gait post-stroke (Hsu, Tang and Jan 2003; Dettmann, Linder and Sepic 1987). While there is no consensus on the reason for a longer paretic step length, there is some evidence that it indicates a greater reliance on the non-paretic leg for weight bearing and less paretic leg propulsion (reduced plantarflexor moment impulse/activation) within the gait cycle (Balasubramanian et al. 2007; Allen, Kautz and Neptune 2011; Kline et al. 2010). Therefore, the significantly greater improvement in step length on the non-paretic limb in the earlier entry group may indicate greater gains in stability, muscle activation, and strength of the paretic limb musculature. This would allow greater paretic limb weight bearing and consequently a longer non-paretic leg step length. Conversely, others suggest that an increase in non-paretic step length indicates a reliance on compensatory behavior learning for adaptation (Kwakkel, Kollen and Lindeman 2004). While paretic-side leg strength remained significantly lower in the later entry group post-training, the similar and significant improvements in leg strength in both earlier and later entry groups also suggests that multiple mechanisms including that related to spontaneous recovery may have accounted for the greater mobility advantage to the early entry group. Further research is required to understand the underlying mechanisms for gait change related to stroke recovery time.

6.1 Limitations and Future Directions

6.1.1 Limitations

The studies included in this thesis add to the literature that provides evidence for the feasibility and efficacy of an adapted CR program for people following stroke. However, there were limitations to these studies. Most of these limitations have been addressed in the respective Chapters. The following section provides a more robust description of some of the limitations.
Chronic Effects of Exercise (Measurement of Ambulatory Function)

With regard to the design of the study in Chapter 4, causal conclusions regarding the impact of a CRP on ambulatory function cannot be drawn from this observational study that did not include a non exercising control group. However, the mean elapsed time following stroke to the start of the intervention was 25 ± 42 months and studies examining the natural history of recovery in mobility suggest that there may be a plateau in recovery approximately 3 months following stroke (Kelly-Hayes et al. 1989; Jorgensen et al. 1995; Wade et al. 1992). For example, in the Copenhagen Stroke study, weekly measures of functional disabilities (ADL measured by the Barthel Index) were conducted in 1,197 patients at the time of stroke admission to the end of rehabilitation, and then 6 months post-stroke (Jorgensen et al. 1995). Results revealed that recovery of walking function occurred in 95% of the patients within the first 12.5 weeks post-stroke. Similarly, Kelly-Hayes et al. (Framingham Heart Study data) measured the time course of functional recovery by change in the Barthel Index in 46 individuals at time of stroke onset, and at 3, 6, and 12 months post-stroke (Kelly-Hayes et al. 1989). These data revealed that there was significant recovery in mobility occurring mostly during the first 3 months post-stroke with little change thereafter. Therefore, the intervention of the current study was introduced in a stable period when spontaneous changes were less likely to occur. Moreover, mobility status has been reported to deteriorate 1 to 3 years post-stroke (van de Port et al. 2006; Paolucci et al. 2001). Yet, while there was no significant baseline difference in 5 meter walking speed and 6 minute walk test distance between earlier and later intervention groups, there was a significant improvement and not deterioration in ambulatory function of the later entry group after 6 months of exercise training.

Chronic Effects of Exercise (Measurement of Cognition)

A limitation of the study conducted in Chapter 5 was related to the use of the MoCA to quantify cognitive function. However, Koski et al. applied Rasch analysis techniques from data gathered from a geriatric outpatient clinic, and reported that the scores from the MoCA can be used to quantify the amount of cognitive ability of an individual and can be used to track changes in
cognition over time (Koski, Xie and Finch 2009). The authors determined that the quantitative measure represented the amount of cognitive ability of an individual and could measure the magnitude of change in the context of clinical trials. Therefore, the benefits of using the MoCA go beyond a qualitative assessment for which it was originally intended.

A further limitation was failure to conduct between observer reliability measures of the MoCA instrument. However, Gill et al. reported that the MoCA demonstrated good inter-rater reliability (intra-class correlation coefficient of 0.81) and test-retest reliability (intraclass correlation coefficient of 0.79) when compared to a neuropsychological battery in the Parkinson’s disease population (Gill et al. 2008). Also, test-retest reliability of the MoCA has been reported as excellent. Correlation between two evaluations (r=0.82) and mean change in MoCA scores from the first to second evaluation has been reported to be 0.9 points (Nasreddine et al. 2005). While we did not estimate inter-tester reliability, we instituted other methods to encourage reliability between observers. For example, the training for administration of the MoCA was conducted by a psychologist, and the two people assigned to administering the MoCA compared outcomes with each other and had informal “calibration” meetings with a psychologist when a score required verification. Although this was not an inter-tester reliability estimate, it likely resulted in improved reliability between raters given that only two of the questions introduced subjectivity (the three-dimensional cube copy, and clock-drawing constructs).

There is some uncertainty as to the most appropriate threshold score on the MoCA for determining mild cognitive impairment in people following stroke. Early research providing the rationale for a threshold score of <26 on the MoCA to determine mild cognitive impairment was conducted in memory clinics where people were at risk for Alzheimer’s disease (Nasreddine et al. 2005; Smith, Gildeh and Holmes 2007; Luis, Keegan and Mullan 2009). More recently, a study conducted by McLennan et al. examined the MoCA for capacity to detect mild cognitive impairment in people at risk for vascular related cognitive impairment (McLennan et al. 2011). McLennan and colleagues describe the rationale for why the sensitivity and specificity of the MoCA for detecting mild cognitive impairment in Alzheimer’s disease may be different from the threshold score for detecting vascular dementia. Mild memory impairments predict the later
development of Alzheimer’s disease but other cognitive domains are better predictors of vascular dementia. McLennan et al. conclude that a threshold of <24 was the most accurate for predicting mild cognitive impairment in individuals with cardiovascular disease. Following this, Pendelbury et al. further defined a more accurate threshold for detecting mild cognitive impairment for individuals in the chronic stage of stroke (Pendlebury et al. 2012). In this study, sensitivity and specificity for mild cognitive impairment were optimal with a MoCA score of <25 (sensitivity 77%, specificity 83%). A study conducted by Damian et al. provide further evidence that lower threshold scores for detecting mild cognitive impairment have higher sensitivity and specificity when there is a higher prevalence of cognitive impairment in the population being assessed as in the stroke population (Damian et al. 2011).

Finally, while the lack of effect that stroke recovery time to initiation of the program had on change in overall cognition in this study suggests spontaneous recovery played an inconsequential role on outcomes, a limitation of this study was the lack of causative evidence provided by correlational evidence. However, more than 80% of the patients started cardiac rehabilitation more than 6 months post-stroke, and while there does not appear to be a consensus on cognitive change, previous research trends towards an indication that unappreciable changes in cognition occur after the first 3 to 6 months of recovery. Data from the Framingham Heart Study (n=46) showed that cognitive function, as measured by the Folstein Mini Mental State Exam, improved significantly during the first 3 months post-stroke with little further change when measured 6 and 12 months post-stroke (Kelly-Hayes et al. 1989). In a prospective study, Cassidy et al. measured the natural recovery of visuospatial neglect in 27 patients with right hemispheric stroke within 7 days of stroke, and monthly thereafter for a total of 3 months (Cassidy, Lewis and Gray 1998). Visuospatial neglect was measured using the Behavioral Inattention Test battery (Wilson, Cockburn and Halligan 1987). While recovery occurred throughout the three month period, improvements were greatest in the first month. Finally, in a large prospective study, Pederson et al. measured the rate of remission of aphasia in 881 patients with acute stroke (Pederson et al. 1995). Assessment of aphasia was conducted at admission, weekly during the course of hospitalization, and then at 6 months follow-up using the aphasia scale of the Scandinavian Stroke Scale instrument (Lindenstrem, Boysen and Christansen 1991). At hospital admission, 38% of the patients had aphasia, and upon discharge the proportion
decreased to 18%. In 95% of patients, stationary language function was reached within 2 weeks of index stroke event in those with initial mild aphasia, within 6 weeks in those with moderate, and within 10 weeks in those with severe aphasia. Of the 331 patients with aphasia at admission, 28% participated in aphasia therapy but there was no difference in recovery between those who did and those who did not participate. Collectively, these studies suggest that while there is variability among recovery of people following stroke (varies by stroke severity), most of the functional improvement occurs in the first 3 months post-stroke, with cognitive improvement sometimes extending beyond 3 months.

**Exercise Adherence Measured by Exercise Log**

Mean AT distance, time, intensity, and heart rate, as well as the RT weight load lifted as ascertained by exercise log were reported in the study presented in Chapter 5. While there are inherent limitations in both self-reported exercise logs for a program utilizing a combination of home and supervised exercise sessions, it is a system that has been used at Toronto Rehab for over 40 years in cardiac patients and 6 years in patients following stroke, and in our experience (and those reported in numerous publications) is a reliable and effective model for the delivery of an exercise rehabilitation program (Hamm and Kavanagh 2000; Kavanagh et al. 2002). In terms of the exercise logs, studies have validated the 7 day recall activity diary against the doubly labeled water method showing that they accurately assess energy expenditure in older and younger populations (Bratteby et al. 1997; Bonnefoy et al. 2001). While we do not use the recall method, patients are required to record information at the time that they do the exercise, eliminating problems associated with recall. Also, an education session dedicated to teaching patients how to fill in the exercise logs and to measure resting and exercising heart rates accurately is conducted at an orientation session. Finally, to ensure accuracy, heart rates that the patient records at home and at the weekly visit to the centre are validated against what is measured by a rehab staff member at each weekly session. Further training is given if required.
Etiology of Stroke

With regard to reporting underlying etiology of atherosclerotic strokes, we were limited by the description of the stroke reported in the medical/hospital notes accompanying the referral information. However, in the study presented in Chapter 5 we further defined the etiology of atherosclerotic strokes as either large artery disease (57%, 4/7), small artery disease (28.6%, 2/7), or etiology unknown (14.3%, 1/7). There were no cardioembolic strokes, and 7 hemorrhagic stroke types.

6.1.2 Future Directions

The results of the studies included in this thesis reveal gaps in the literature and raise questions that require further investigation and will be discussed in this section. Specifically, while the results from the studies presented herein provide compelling evidence for the benefit of combined AT and RT in an adapted CR program, further research is required to elucidate the type(s) of exercise that will contribute most to recovery following stroke. In addition, we uncovered sex differences in referral to CR programs and a mitigated utility of baseline CPETs for prescribing exercise to women compared to men at program entry that require examination. Also, a series of studies are required to determine barriers to referring people post-stroke to CR programs and issues that may prevent the integration of adapted CR programs as a sub stream of the traditional CR model. The studies presented within this thesis included only patients with mild to moderate motor deficits able to walk at least 10 meters with or without a gait aide. Studies to pilot alternative exercise program models to treat those with severe neurological deficits and for others unable to participate in a group and/or facility based program are needed. Finally, an issue to be addressed is related to the additional resources required to institute a TRI-REPS style program when compared to traditional CR programs. In view of the present economic environment, data linkages studies are required to determine if there are downstream health services utilization and survival benefit for those post-stroke who attend a CR program compared to those who do not. Results of these investigations would help to garner further support for the integration of structured exercise and secondary prevention programs into the traditional CR program model for those recovering from stroke.
Type of Exercise

Research conducted in chronic disease and healthy populations suggest that AT and RT “combination therapy” may produce synergistic and superior effects along cognition, cardiovascular fitness, and mobility domains, when compared to AT alone (Marzolini, Oh and Brooks 2012; Marzolini et al. 2008; Colcombe and Dramer 2003; Smith et al. 2010). However, while meta-analyses comparing AT vs. control and AT+RT vs. control in people post-stroke show both exercise interventions result in significant improvements in $\dot{V}O_2\text{peak}$, mobility, and cognition these interventions have not been compared to each other (Brazzelli et al. 2011; Brazzelli et al. 2012; Colcombe and Dramer 2003; Smith et al. 2010). Moreover, a combined training approach appears to be superior for HRQoL benefit. A recent meta-analysis reported that only studies that included combined RT and AT interventions had a significant effect on HRQoL post-stroke with no change as a result of studies that included AT alone interventions (Chen and Rimmer 2011). Therefore, evaluating the effects of an exercise program in people with motor impairments post-stroke randomized to either combined AT+RT or AT alone on cognition and other parameters of stroke recovery would help to elucidate treatment strategies to address impairments and support modifications to program delivery models.

Predictors of Treatment Response

The demographic and physiological factors that predict aerobic and resistance training induced changes on $\dot{V}O_2\text{peak}$ and ADL function have remained largely unexplored. Knowledge of the importance of these determinants would aid in selecting treatment strategies for improving $\dot{V}O_2\text{peak}$ and ADL function in stroke survivors. Therefore, exploring clinical and demographic factors that predict treatment response (change in $\dot{V}O_2\text{peak}$ and ADL function (functional ambulation and sit and stand performance)) in individuals following a stroke participating in a 6 month AT and RT program would be of clinical significance. Independent variables would include muscular strength (knee flexion and extension, dorsi- and plantar flexion), body composition (fat-free mass and fat mass), joint range of motion (hip flexion), depressive symptoms, fatigue, cognitive
function, gait characteristics, size and location of stroke, exercise duration and intensity as well as demographic factors. Knowledge of the importance of these determinants would aid in selecting treatment strategies for improving $\text{VO}_2\text{peak}$ and function in stroke survivors.

**Sex Differences**

Several sex differences were revealed in the study presented in Chapter 2 examining utility of the CPET for prescribing exercise to people following stroke. Among the sample of consecutively enrolled patients referred to CR, a significantly smaller proportion of participants were women (30% of all referrals). As reported in the Discussion section, incidence of stroke is higher in women in the general population suggesting that the proportion of referrals to CR should be at least the same, if not greater for women than men (Seshadri et al. 2006; Rosamond et al. 2008). Also, as observed in the study in Chapter 2, women referred to CR were younger when compared to age at time of first ever stroke (Petrea et al. 2009). This suggests a bias towards younger women being referred to CR. Because younger women may have less disability and greater functional capacity, the entry criteria to the CR program may have contributed to the younger age of women at entry to CR. Exploration of the sex difference in referral to secondary prevention and exercise programs merits investigation so that barriers can be removed, providing equal access to care following TSR. Our results strongly suggest the need for focused exploration of barriers to participation in this population given the demonstrated benefit to women observed in the included studies. Another sex difference that was uncovered was the mitigated utility of the baseline CPET for prescribing exercise to women compared to men. The underlying reason(s) and possible strategies to provide a more effective rehabilitation process for women should be pursued.

**Exercise Program Related Studies: Barriers to Referral and Integration of Adapted Exercise Programs for People following Stroke within the Traditional CR Model**

While the program model of the TRI-REPS program has advanced over the 6 years since inception, improvements informed through research and experience continue to occur with the
goal of creating a program template or “tool-kit” to guide other CR programs in developing programs tailored to meet the needs of people following stroke. Future studies to improve the program model include examination of the effects of a peer support program on patient satisfaction, quality-of-life, and domains of depression and anxiety. Also, integrating chronic disease self-management program components into the adapted CR program model may result in better day-to-day long-term self-management of health issues, improved self-efficacy, reduced health service utilization costs and ongoing modification of risk factors and thus is an intervention that warrants investigation.

Questionnaire based studies or focus groups held with Program Managers of CR programs across Ontario would help to identify barriers to incorporating adapted CR services for people following stroke within the traditional CR program. First, a survey would assess secondary prevention services currently available to Ontarians who are recovering from a stroke event. Second, a better understanding of the perceived barriers to including people following stroke with neurological impairments and potential solutions to close the current gaps in secondary prevention and rehabilitation care for those recovering from stroke. The findings would facilitate the development of recommendations for future research, demonstration projects and policy changes. Potential barriers within CR programs could be explored such as lack of trained personnel to manage patients with stroke, lack of appropriate exercise equipment for patients with disability in the CR facility, requirement of an additional exercise class separate from those without stroke, lack of additional resources, lack of infrastructure for patients with mobility issues (elevators, ramps, railings for stairs), increased risk of falls perceived to prohibit exercise in patients following stroke, increased risk of falls requiring greater staff to patient ratios than traditional CR programs, belief that there is little to no evidence that stroke patients with physical impairments would benefit from an exercise program.

Focus group and/or questionnaire based studies to determine barriers to referring patients to CR programs administered to health care professionals (i.e. inpatient/outpatient physiotherapists, physicians) would help to identify barriers that may be modifiable. Patient-related barriers that would merit exploration include transportation issues, musculoskeletal, joint problems or other comorbidities that may be perceived as a reason for non referral, work responsibilities, lack of
interest, lack of confidence, severe depressive symptoms, severe fatigue, family and care giving responsibilities, distance to CR facility, language barriers, severe cognitive dysfunction, financial issues, lack of caregiver support at home or to accompany to CR session, severe neurological deficits and not meeting minimal requirements of program (i.e. ability to walk at least 10 meters with or without a gait aid).

Alternative program models to accommodate people with severe neurological impairments that would preclude them from participating in a group based program should be explored. One such model is a home-based approach guided by CR personnel communicating with patients remotely by phone or video conferencing with assistance provided to the patient by a caregiver. Often caregivers are unable to attend regular class times offered by CR programs, and thus offering a flexible time to communicate and receive guidance from the CR staff member while the patient is at home would offer an alternative to the traditional model. The exercise program would be prescribed during one face-to-face session, establishing exercises appropriate for the functional level of the patient, guided by ECG telemetry if a CPET is not feasible. This type of study would build on research examining alternative models of care conducted by others (Olney et al. 2006).

6.2 Conclusions

We have demonstrated that given the elevated risk for recurrent stroke and coexisting CAD, the exercise training components as well as risk factor interventions and assessments such as the CPET offered by interprofessional health care CR teams are appropriate for people following stroke and result in favorable outcomes in domains of functional ambulation, cardiovascular fitness, muscular strength, sit-to-stand performance, and cognitive function important in the stroke recovery process.

The rate of clinically relevant abnormalities in those with or without a diagnosis of coexisting CAD uncovered by CPET support the translation to practice of the American Heart Association recommendation to include an exercise stress test with ECG monitoring prior to initiating an exercise program following stroke (Furie et al. 2011). Further changes to the program delivery
model based on the research presented, would be to include a CPET mid program to determine a more efficacious exercise prescription for women following stroke. Also, based on our findings, we recommend that on days when AT is carried out alone, exercise duration should be extended to approximately 40 minutes to meet energy expenditure guidelines. We also recommend that in view of the small proportion of patients reaching a true physiological maximum on the CPET (\(\dot{V}O_2\text{max}\)), a greater reliance on the VAT for prescribing exercise should be considered as it is a more easily achievable and a more metabolically relevant measure than \(\dot{V}O_2\text{peak}\) that also reflects cerebral metabolism. By so doing, practitioners will avoid prescribing an intensity that may be inadequate and as our research suggests, will have a greater potential for cognitive gain. Also, the focus of treatment following stroke has traditionally been on the affected limbs. We have shown the importance of not neglecting the limbs unaffected by stroke. Building total body muscle mass is important not only for better metabolic control in those with diabetes and insulin resistance (Cuff, Meneilly and Martin 2003; Sigal et al. 2007), but also for improving cognitive function. Finally, patients should be referred to CR immediately following TSR for greater mobility advantage and to avoid the deterioration in paretic and non paretic-side leg strength that appears to occur with time.

Given the demonstrated benefits of adapted CR for people with mild to moderate motor impairment following stroke and the limited opportunities for accessing a structured physical activity program, policies to incorporate such programs within the health care setting are needed. CR programs offer multiple CPET modality options as well as the experience and training to assess and manage patients with multiple comorbidities that may not exist in other facilities. CR programs have the unique opportunity and are well positioned to fill the existing gap in the care of those recovering from stroke. With the increasing rate of modifiable risk factors and a growing elderly population, it is estimated that the number of people living with stroke will grow (Gillum and Sempos 1997). Individual care, specifically related to exercise training programs are inadequate, and more research is needed to determine exercise treatment strategies that will result in the most favorable outcomes for people following stroke.
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Appendix A  Additional Information and Analyses

Chapter 2: The analyses of the ability of individuals to achieve at least one of the critical exercise intensities on the CPET analyzed by time from stroke to baseline CPET, did not result in a significant group difference as shown in the table below.

Table A1. Analysis of the Utility of the CPET by Time from Stroke to Baseline CPET

| Utility of CPET | Time from Stroke to Baseline CPET | | | |
|----------------|---------------------------------|---|---|---|---|
| ≥1 of VAT, $\dot{V}O_2^{max}$, or CRA, n (%) | 12 to 24 weeks | 25 to 52 weeks | > 52 weeks | P value |
| Baseline CPET | 15/21 (71.4) | 26/36 (72.2) | 26/41 (63.4) | 0.7 |
| 6 month CPET | 18/20 (90) | 27/29 (93.1) | 27/36 (75) | 0.1 |
| Baseline VO2peak, ml/kg/min | 14.7±4 | 16.1±5.1 | 14.6±4.4 | 0.4 |
| Change in VO2peak, ml/kg/min | 2.1±3.1 | 3.0±3.4 | 2.1±2.3 | 0.4 |

CPET=Cardiopulmonary exercise test, VAT=ventilatory anaerobic threshold, CRA=clinically relevant abnormality, VO2peak, ml/kg/min= Peak oxygen uptake, milliliters/kilogram/minute.

Sample Size Calculation:

There have been no previous studies in healthy or chronic disease populations that have examined the utility of the CPET for prescribing exercise. Thus there is no previous data for which to calculate a sample size. Therefore, the analyses for this study included the maximal number of cases possible.

Chapter 3: Energy expenditure and amount of time exercising at minimal target exercise intensities reported to elicit health benefits was not affected by beta-blocker medication prescription as seen in Table A2. Several studies have shown that beta-blockade medication does not affect oxygen uptake at peak effort or at an absolute submaximal exertion level such as the anaerobic threshold, or peak workload. (Wittke and Kemmler 1999; Sklar et al. 1982; Wonischa et al. 2003) The chronotropic and inotropic responses are compensated for by a concomitant increase in stroke volume (Reybrouck, Amery and Billiet 1977), an increase in left
ventricular diastolic filling pressure (Poulsen, Jensen and Egstrup 2000), and an increase in oxygen extraction in the peripheral working muscles (Frisk-Homberg, Juhlin-Dannfelt and Astrom 1985). Therefore, it is unlikely that beta-blockade medications would affect energy expenditure which is calculated from oxygen uptake, or the relative measures of oxygen uptake that are reported in the present study. One of the rationales for using oxygen uptake as a measure of intensity in this study rather than heart rate response was that heart rate is a poor reflection of exercise intensity in this population. It is not uncommon for stroke survivors to be prescribed medications (beta-blockade) that have varying effects on the heart rate response to exercise throughout the day, rendering the relation between heart rate and exercise intensity difficult to interpret. Moreover, the heart rate/VO$_{2peak}$ relationship will vary when exercising in hot humid conditions, between different modes of exercise, in an altered hydrated state, and during sustained static exercise (reduced venous return and activation of baroreceptor reflex) (Smith and Mitchell 1995).

Other medications prescribed to patients in this study also do not have an effect on peak exercise capacity as reported by the American College of Sports Medicine (ACSM 2009), including angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blocker (Norvasc/Amlodipine) or Antilipidemic agents such as Lipitor.

**Table A2. Effect of Beta-blocker Medication Prescription on Energy Expenditure and Amount of Time Exercising at Minimal Target Exercise Intensities**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta-blocker N=4</th>
<th>No Beta blocker N=12</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Kcals</td>
<td>252.9±31.5</td>
<td>251.7±55.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Total time time ≥40% of VO$_{2peak}$, minutes</td>
<td>50.6±7.8</td>
<td>46.7±10.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Total time ≥3 METS, minutes</td>
<td>30.2±12.1</td>
<td>31.0±12.8</td>
<td>0.9</td>
</tr>
</tbody>
</table>
Sample Size Calculation (Single Sample T-test statistic):

*Ability of stroke survivors to reach minimal exercise recommendations:* The main comparisons in this analysis was the amount of time per exercise session in the exercise training zone (≥40% of VO$_{2peak}$) compared to the recommended minimum duration of 20 minutes for stroke survivors as per AHA Guidelines (Gordon et al. 2004). However, as there are no previous studies in the stroke or cardiac populations measuring this outcome the sample size calculation used data from cardiac studies examining the average exercise energy expenditure (kcals) per exercise session. This was compared to the recommendation of 200 kcals of exercise energy expenditure (ACSM 2009; Franklin, Swain and Shephard 2003; Hambrecht et al. 1993). Research data shows that the average number of kcals expended by patients with CAD in a cardiac rehabilitation session measured 299±161 kcals (Ayabe et al. 2004). In view of the physical and neurological impairments of stroke survivors, we estimated a mean kcal expenditure of 220 fewer kcals. The magnitude of the difference to the target of 200 kcals per session would therefore be 120 kcals. For the typical stroke patient at TRI who is at high risk for recurrent stroke and CAD, extremely deconditioned and overweight, expending less than half of the recommended kcals per session would be clinically important. The estimated SD would be similar to the CAD population (161 kcals).

$$\sigma = \pm 161 \text{ kcals (standard deviation)}$$
$$\Delta = \pm 120 \text{ kcals (magnitude of difference in estimated kcals from recommended)}$$
$$Z_{\beta} = 1.28 \ (80\% \ power \ desired, \ \beta = 0.20)$$
$$Z_{\alpha} = 1.96 \ (two \ tailed; \ p<0.05)$$

Therefore, a sample of 16 subjects would be needed for this comparison.

Chapter 4:

Sample Size Calculation:

*Physiological Outcomes in People following Stroke Attending an Adapted Cardiac Rehabilitation Program: Does Time from Stroke Make a Difference?*

One of the main comparisons of this study was the potential difference in change in cardiovascular fitness between those referred early vs. later following the index stroke event.
Therefore, the sample size was based on the potential of a clinically relevant difference in change in VO$_{2\text{peak}}$ between groups of 1.5 mL·kg·min$^{-1}$ or 10-15%. Given that the mean VO$_{2\text{peak}}$ of people following stroke is approximately 15 mL·kg·min$^{-1}$, this would be sufficient to elevate cardiovascular fitness (18 mL·kg·min$^{-1}$) above the threshold level required to perform basic and some instrumental activities of daily living.

- $\sigma = \pm 2$ mL·kg·min$^{-1}$
- $\Delta = \pm 1.5$ mL·kg·min$^{-1}$
- $Z\beta = 1.28$ (80% power desired, $\beta = 0.20$)
- $Z\alpha = 1.96$ (two tailed; $p<.05$)

Therefore, a sample of $\geq 31$ subjects for each of the two groups (≤1 year post-stroke and > 1 year post-stroke) would be required to detect a significant difference between groups in VO$_{2\text{peak}}$ (1.5 mL·kg·min$^{-1}$) with a power of 0.8 for this study. However, due to the drop out rate of patients participating in TRI-REPS in a previous study (~10% over 6m), a sample size of 34 patients for each group would be necessary. This sample size would also be sufficient to detect a difference of at least 30 metres between groups in the 6MWT.

Additional Analysis:
An alternative analysis to that presented in Chapter 4 to determine the effect of the amount of time elapsed from the index stroke event to the start of the intervention was conducted. The time from stroke data did not meet the assumption of normal distribution and thus the data was log transformed. The relationship between change in the primary outcome measures and “time from stroke” (weeks) were determined using the Pearson correlation coefficient. Only change in six minute walk distance was significant ($p<0.05$). A linear regression model was fitted, regressing the domain of change in six minute walk distance with “time from stroke” controlling for age, sex, baseline measures of the following: body mass index, CMSA (leg, foot, arm, hand), Berg score, CESD score, VO$_{2\text{peak}}$, paretic-side leg strength, fast paced walking cadence, and six minute walk distance. We selected a final model forcing “time from stroke” in the respective model and selecting variables into the model if it changed the crude “time from stroke” parameter estimate more than 15%. Probability values $<0.05$ were considered significant. All analyses were performed in SPSS (version 19.0, SPSS, Inc., Chicago, IL). Analysis revealed that there was a negative correlation between change in six minute walk distance and “time from
stroke” (β= -42.107, p=0.002) and explained 12.2% of the variance in change in six minute walk distance independent of the following baseline variables: age, sex, body mass index, CMSA (leg, foot, arm, hand), Berg score, CESD score, VO2peak, paretic-side leg strength, fast paced walking cadence, six minute walk distance.

Chapter 5: Reported in the table below is the Pearson correlation coefficient (r) between change in MoCA scores and change in regional and total body FFM. In Chapter 5, we reported that “in a linear regression model there was a positive association between change in cognitive function and change in fat-free mass of the non-affected limbs (β=0.002, p=0.005) …independent of age, sex, time from stroke, and change in fat mass and depression score.”

However, in the linear regression model, there were also significant and independent associations between change in MoCA score and change in appendicular fat-free mass (β =0.001, p=0.02) independent of age, sex, time from stroke, and change in fat mass and depression score. However, change in fat-free mass of the non-affected limbs explained more of the variance (16.5%) in change in MoCA score than did change in appendicular FFM (11.9%).

There was a significant positive association between change in total cognition score and both change in fat-free mass of the non-affected limbs (β=0.002, p=0.005) and change in total appendicular fat-free mass (β =0.001, p=0.02) independent of age, sex, time from stroke, change in fat mass and baseline or change in depression score. However, change in fat-free mass of the non-affected limbs accounted for a greater proportion of the variance in change in cognition score (16%) than did change in appendicular fat-free mass (11.9%).
Table A.3. Association Between Change in Regional and Total Fat Free Mass with Change in Cognition Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Appendicular</th>
<th>Limbs (NA)</th>
<th>Limbs (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoCA score, r (p)</td>
<td>0.3(0.03)</td>
<td>0.38(0.02)</td>
<td>0.43(0.005)</td>
<td>0.26(0.1)</td>
</tr>
<tr>
<td>Visuospatial/executive</td>
<td>0.1(0.5)</td>
<td>0.2(0.2)</td>
<td>0.2(0.2)</td>
<td>0.2(0.2)</td>
</tr>
<tr>
<td>Attention/concentration</td>
<td>0.1(0.4)</td>
<td>0.06(0.7)</td>
<td>0.1(0.5)</td>
<td>0.02(0.9)</td>
</tr>
<tr>
<td>Naming</td>
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<td>0.2(0.3)</td>
<td>0.2(0.3)</td>
<td>0.1(0.4)</td>
</tr>
<tr>
<td>Language</td>
<td>0.1(0.4)</td>
<td>0.1(0.4)</td>
<td>0.08(0.6)</td>
<td>0.2(0.3)</td>
</tr>
<tr>
<td>Abstraction</td>
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<td>-1(0.5)</td>
<td>-0.1(0.5)</td>
<td>-0.1(0.5)</td>
</tr>
<tr>
<td>Delayed Recall</td>
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<td>0.2(0.4)</td>
<td>0.2(0.3)</td>
<td>0.1(0.5)</td>
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<tr>
<td>Orientation</td>
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<td>0.1(0.5)</td>
<td>0.2(0.2)</td>
<td>0(1)</td>
</tr>
</tbody>
</table>

NA=non-affected, A=affected

Sample Size Calculation:
Sample size for proportions in repeated measures: We estimated that the baseline rate of mild cognitive impairment would be 66% according to reports in the stroke population (Ya-Ping et al., 2006); after the exercise intervention we estimated that a clinically meaningful change in the proportion of people with mild cognitive impairment would be a reduction of 26 percentage points (to 40%). Therefore, with a Type I error = 0.01 and with 80% power, the sample size required would be 40 patients.

APPENDIX B  Aerobic Exercise Intervention for TRI REPS Program

3.2.1 Aerobic Exercise: The AT prescription is based on data from the graded exercise test conducted at entry to the program (see section 4.1). The goal of the AT prescription is for the patient to progress to 20 to 60 minutes of exercise, 5 times per week at an intensity equivalent to a combination of the following:

- 40 to 70% of peak oxygen uptake
- 40 to 70% of heart rate reserve
- The heart rate or oxygen uptake achieved at the ventilatory anaerobic threshold
- Rating of Perceived Exertion of 11 to 14 on the Borg 6 to 20 Scale (Borg 1982)

MODE: Walking and stationary recumbent or upright cycling are the common modes of aerobic exercise prescribed to patient recovering from stroke at the TRI-REPS program. When prescribing the mode of exercise two criteria are considered. First, the patient should have access to the exercise equipment when not at the rehab clinic. Second, the patient should be able to achieve a heart rate as close as possible to a minimum of 40% of heart rate reserve or the heart rate achieved at the anaerobic threshold as measured on the graded exercise test without discomfort or aggravation of any musculoskeletal conditions. If exercise other than walking is prescribed, then walking as tolerated is included either as the cool down exercise or performed at a different time of day to the main exercise session.

INTENSITY: This is the most important parameter of the prescription both from a safety and efficacy point-of-view. The initial prescription is based on a heart rate range from a combination of the following: approximately 40 to 70% of heart rate reserve; the heart rate at 40 to 70% of peak oxygen uptake; and/or the heart rate at which the anaerobic threshold occurred. If there are any abnormalities on the test (i.e. ST segment depression, angina, drop in blood pressure, dyspnea etc.) the heart rate range will be set below this level ensuring that the patient is exercising at a safe intensity.

Patients who do not have any neurological problems that would affect their gait will be prescribed a walking pace estimated to require either an oxygen uptake equivalent to 40 to 70% of the peak oxygen uptake attained on the GXT and/or the walking pace that requires the oxygen uptake occurring at the anaerobic threshold. A heart rate range is also prescribed but for those patients taking Beta Blockade medication is to be used as a guideline for exercise intensity in combination with a rating of perceived exertion (RPE) of 11 to 14 (light to somewhat hard).
APPENDIX C Resistance Training Prescription for TRI REPS Program

TRI-REPS Program

Resistance training (RT) is very important for patients recovering from a stroke and does not have any adverse effects on muscle tone on the paretic (weaker) limb. Benefits can include improved blood sugar control in people with diabetes and pre-diabetes, favorable changes in balance, motor control, strength in both affected and non-affected limbs, and ability to perform activities of daily living such as stair climbing and sit-to-stand performance. In addition it is possible that strengthening the muscles and connective tissue around each joint may decrease the risk of musculoskeletal injuries resulting from abnormal gait patterns, as well as increasing gait speed and decreasing the risk of osteoporosis (especially important in the affected limbs).

Design:

The choice of RT exercises and type of equipment are based on the patient’s goals, gait pattern, grip strength, joint range of motion, presence or degree of hypertonicity, and balance. We recommend a combination of hand held dumbbells, dynabands (with wrist and ankle attachments), and the patient's body weight for resistance. These types of RT exercise will allow for independent limb actions and weight prescription. The exercises should be task specific, incorporating muscle actions that are performed during ADLs emphasizing re-training of balance and coordination, body weight support, weight shifting, and incorporating multi-joint rather than single-joint movements.

Eight to 11 exercises should be prescribed, targeting all major muscle groups. Owing to increased risk of falls, complex, multi-joint exercises that require increased balance control should be performed at the beginning of the exercise session when fatigue is less of an issue. Abdominal and trunk stabilizing exercises, which are required during these earlier activities for maintaining balance, should be included at the end of program. Patients should be advised to perform RT 2 to 3 times per week on non-consecutive days. Exercises should be prescribed in the following order: alternating a lower body exercise with an upper body exercise to prevent
pooling of blood in the extremities, large muscle before small muscle groups, and abdominal and trunk stabilizing exercises at the end of program as they are required for balance and should not be fatigued early in the program. Multi-joint exercises that require balance should be performed at the beginning of the program as they are more neurologically complex and should not be performed when fatigued.

Patients should be advised not to hold their breath when performing exercises and to avoid isometric contractions (including holding weights tightly) as this will result in an elevated blood pressure response. If the systolic blood pressure is >220 mm Hg or the diastolic blood pressure >115 mmHg measured during performance of the last 3 repetitions, the weight load or number of repetitions should be decreased. Patients with heart failure or borderline hypertension should be prescribed single limb exercises to mitigate elevations in blood pressure and afterload on the heart. Patients with heart failure should not be prescribed exercises requiring a supine position.

Progression:

Progression of RT exercise (increasing number of repetitions or weight lifted) is essential in order to benefit from the program. A heavier weight enhances muscle fibre recruitment, neural stimulation, and muscle mass accretion (a key physiological adaptation in the control of blood sugars). When possible, prescribe bilateral exercises (e.g. alternating knee raises or bicep curls) thereby increasing coordination between both hemispheres of the brain which may induce reorganization of motor networks and enhanced function. Performing exercises at a fast velocity may increase spasticity of movement. However patients with spasticity should be encouraged to progress selected RT exercise by gradually increasing velocity of movement to reproduce contraction speeds of ADLs and possibly reduce co-contractions. These patients may need to have the limb manually moved for the first few repetitions and then allowed to finish the set under their own control. It is common for patients post-stroke to rely on visual cues for maintaining balance. Therefore, encourage patients to refrain from looking at their lower limbs during lower body exercises to promote enhanced proprioception.
Exclusion Criteria:

- Resting hypertension (SBP > 160 mmHg or DBP > 100 mmHg)
- Hernia (except hiatus)
- History of diabetes with severe proliferative retinopathy

Some General Guidelines:

- Patients should avoid isometric contractions (including holding weights tightly)
- Advise patients not to hold breath when performing exercises.
- Decrease weight if SBP > 220 mmHg or DBP > 115 mm Hg measured during lifting.
- Patients with heart failure or borderline hypertension should do single limb exercises. Patients with heart failure should also avoid supine exercise.
- Coronary Artery Bypass Surgery: Start moderate to heavy RT 3 months after surgery (50-60% of 1 RM)
- Myocardial Infarction (MI): Light weights 2 weeks after MI. Start traditional RT 5 weeks after MI (50-60% of 1 RM).
- Angina: Patients will be less likely to experience angina with RT than with aerobic training.

Volume:

- 1 to 2 sets
- 8 to 11 exercises
- 50-60% of 1 Rep Max (1RM) when possible or RPE of 11-15
- 10 to 15 reps,
- to 3 x per week

Techniques for Prescribing RT Weight Load:

A) One Repetition Maximum Testing (1RM)
**Why do 1 repetition maximum (IRM) testing?**

The RPE method of weight prescription results in a weight of approximately 30-40% of 1 RM. This is the minimum intensity that will result in an increase in strength but will probably not be adequate for significant body composition changes. Therefore, when possible 1 RM testing should be performed. Refer to RPE scale technique for alternative method of weight prescription described below.

**Who should not perform 1RM test**

- Musculoskeletal problems that might be aggravated by a maximal lift
- Severe hemiparesis (IRM should be performed on non-paretic limb only)
- Poor lifting technique
- Other conditions discussed on an individual basis

**Procedure**

1. Patient performs 3 repetitions with the weight established by the RPE method in the previous week or as decided by the staff member. The patient rests 1 - 2 minutes.

2. Patients with hemiparesis should be tested on both sides if possible.

3. Increase the resistance and perform a single repetition, rest 1 - 2 minutes

Repeat #3 until the patient is unable to perform a single repetition.

*Watch for signs of patient approaching biomechanical maximum, such as using other muscles to help lift the weight, compensation for weight using other muscle groups, and breath holding. Advise the patient not to struggle with the weight if they reach a ‘sticking’ point. The last weight lifted using the correct form is the 1 RM score. Use the chart on the following page to determine 50-60% of the one repetition maximum.*
CAUTION: Any more than five, 1 RM trials for one exercise may lead to an inaccurate score due to fatigue. After completing 1 RM testing, the patient should perform one set of each of the exercises at the new intensity (50-60% of 1 RM).

1 REPETITION MAXIMUM TESTING:

<table>
<thead>
<tr>
<th>1 RM</th>
<th>Weight Load 50-60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>5-8</td>
</tr>
<tr>
<td>15</td>
<td>8-10</td>
</tr>
<tr>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>30</td>
<td>15-20</td>
</tr>
<tr>
<td>35</td>
<td>20</td>
</tr>
<tr>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>45</td>
<td>25-30</td>
</tr>
<tr>
<td>53</td>
<td>30</td>
</tr>
<tr>
<td>58</td>
<td>35</td>
</tr>
<tr>
<td>63</td>
<td>35-40</td>
</tr>
<tr>
<td>68</td>
<td>40</td>
</tr>
<tr>
<td>73</td>
<td>45</td>
</tr>
<tr>
<td>78</td>
<td>45</td>
</tr>
</tbody>
</table>

B) Rating of Perceived Exertion Technique (RPE)

1. Patients lift an assigned weight for 10 reps
2. Exercise is repeated with a heavier or lighter weight until the last repetition is rated 12 to 15 on the Borg R.P.E. 6-20 scale*

*Data from TRI show that this technique results in a mean intensity of 40% of 1RM with RPE of 12

Instructions for Helping Patients Progress:
At each rehab class the staff member should ask each patient whether they are performing RT twice per week, experiencing any fatigue or discomfort, and progressing appropriately by gradually increasing the number of repetitions and/or weight lifted.

1. ↑ to 2 sets of 10 reps or remain at 1 set (depends on energy, motivation of patient)*
2. Gradually increase reps to 15,
3. Then increase weight and reduce reps to 10
4. Repeat process

*Note: multiple sets will result in approximately twice muscle mass accretion of single set RT.

When the patient is lifting 2 sets of 15 reps with an RPE of 13/14 or less, suggest that the patient tries a heavier weight/thicker dynaband or adds weight to the squat and heel raise, or increases velocity of movement. Subsequently the repetitions are decreased to 10. To make the exercises in which the patient is using their body weight for resistance more challenging, perform with less or no external support (e.g. progress from static lunge exercise to lunging overground for a distance of 50 metres).

If the patient is finding that he/she is too fatigued and/or doesn’t have enough time for exercise, have patient do half of the exercises one day and the rest on the following day. This would take an extra 10 minutes a day. Repeating the 1 RM test every 3 to 6 months will help for re-assessment of a safe, effective training intensity.
Toronto Rehabilitation Institute: Risk Factor Modification and Exercise Program Following Stroke (TRI-REPS)

Resistance Training

Procedure:

Five minutes of slow walking and a stretching routine should be carried out prior to and after resistance training.

All exercises are to be performed slowly while breathing normally. Lift weight to a count of 2 and lower to a count of 3.

Resistance training should be done 2 times per week with at least one day of rest in between workouts.

A minimum of 30 - 60 sec. of rest should be taken between sets.

If any symptoms occur, discontinue exercise and consult your Rehab Supervisor.

Definitions:

A. Repetition - The performance of one complete exercise movement

B. Set - A fixed number of repetitions (eg. 10 curl ups = 1 set)

C. Circuit - Series of selected exercises
**Progression:**
Perform 1 circuit in the first 2 weekly sessions increasing to 2 circuits in the third weekly session.

When you are able to do 2 sets of 10 repetitions comfortably, gradually increase the number of repetitions to 15 *(this may take 2 to 3 weeks).* When you are able to perform 2 sets of 15 repetitions comfortably (RPE of 11 - 13) then increase the weight by 2 to 5 lbs. or increase Thera-Band thickness** and reduce the repetitions to 10. The last repetition performed of an exercise should not be rated any higher than 15 on the RPE scale. After completing a set, it should feel as if 2 to 3 more repetitions could be done, but not 5 to 10 more.

When 15 repetitions of the ‘curl up’ can be done comfortably (RPE 11-13) then cross arms over chest. When 15 repetitions of these can be done comfortably, put fingertips to temples with elbows extended out.

To progress with the ‘standing squat forward raise’ and ‘heel raise’, hold 5 to 10 lb. weights at your side with a ‘palms-in’ grip. Perform the exercise keeping weights at your side.

Continue to fill in resistance training diaries, handing them in when attending regular exercise class.

**Example of Progression:**

<table>
<thead>
<tr>
<th>Week</th>
<th>Sets</th>
<th>Repetitions</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2</td>
<td>10</td>
<td>↔ lbs.</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>↑12</td>
<td>↔ lbs.</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>↑14</td>
<td>↔ lbs.</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>↑15</td>
<td>↔ lbs.</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>↓10</td>
<td>↑ lbs.*</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>↑11</td>
<td>↔ lbs.</td>
</tr>
</tbody>
</table>

*Progression of weight in pounds (hex dumbbells)
1→2→3→4→5→8→10→12→15→20→25→30→40→45→50

**Follow same progression with exercise bands. Lowest to highest resistance is yellow > red > green > blue > black

**Note:** People will progress at different rates. This is an example only.