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Ventilatory Threshold may be a More Specific Measure of Aerobic Capacity than Peak Oxygen Consumption Rate in Persons with Stroke

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Abstract

Background—After stroke, aerobic deconditioning can have a profound impact on daily activities. This is usually measured by the peak oxygen consumption rate achieved during exercise testing (VO₂-peak). However, VO₂-peak may be distorted by motor function. The oxygen uptake efficiency slope (OUES) and VO₂ at the ventilatory threshold (VO₂-VT) could more specifically assess aerobic capacity after stroke, but this has not been tested.

Objectives—To assess the differential influence of motor function on three measures of aerobic capacity (VO₂-peak, OUES and VO₂-VT) and to evaluate the inter-rater reliability of VO₂-VT determination post-stroke.

Methods—Among 59 persons with chronic stroke, cross-sectional correlations with motor function (comfortable gait speed [CGS] and lower extremity Fugl-Meyer [LEFM]) were compared between the different aerobic capacity measures, after adjustment for covariates, in order to isolate any distorting effect of motor function. Reliability of VO₂-VT determination between 3 raters was assessed with intra-class correlation (ICC).

Results—CGS was moderately correlated with VO₂-peak ($r=0.52$, $p<0.0001$) and weakly correlated with OUES ($r=0.41$, $p=0.002$) and VO₂-VT ($r=0.37$, $p=0.01$). LEFM was weakly

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correlated with VO₂-peak ($r=0.26$, $p=0.055$) and very weakly correlated with OUES ($r=0.19$, $p=0.17$) and VO₂-VT ($r=0.14$, $p=0.31$). Compared to VO₂-peak, VO₂-VT was significantly less correlated with CGS (r difference = -0.16 , $p=0.02$). Inter-rater reliability of VO₂-VT determination was high (ICC: 0.93, 95%CI: 0.89 to 0.96).

Conclusions—Motor dysfunction appears to artificially lower measured aerobic capacity. VO₂-VT seemed to be less distorted than VO₂-peak and had good inter-rater reliability, so it may provide more specific assessment of aerobic capacity post-stroke.

Keywords

stroke; exercise testing; aerobic capacity; motor function; paresis; deconditioning

Introduction

Among persons with stroke, cardiopulmonary deconditioning (decreased aerobic capacity) is a common condition that can limit performance of daily activities and increase the risk of future cardiovascular events.^{1,2} The gold standard measure of aerobic capacity is the physiologic maximum oxygen consumption rate (VO₂-max), which is assessed with a maximal-effort graded exercise test (GXT) and gas exchange analysis.³ In clinical populations, this measure is commonly termed VO₂-peak to acknowledge that the participant may not have reached maximal aerobic capacity due to other limiting factors such as limb fatigue or low motivation.³

VO₂-peak is the most common measure used to assess aerobic capacity in stroke research.^{1,2,4} A systematic review involving studies of mild to moderate stroke found that mean VO₂-peak ranged from 8 to 22 mL/kg/min, which represented 26% to 87% of normative values.⁴ These low values seem to indicate that aerobic deconditioning represents a primary cause of disability after stroke that severely limits performance of daily activities,^{1,2,5} especially when combined with the elevated metabolic cost of mobility in this population.⁶ However, VO₂-peak may be largely determined by motor function (rather than aerobic capacity) after stroke,⁷ as GXTs can be limited by motor dysfunction (e.g. paresis),⁸ and this can occur well before VO₂-max is reached. For example, in a study of 98 consecutive patients at least 3 months post stroke that were enrolled in a cardiac rehabilitation program, only 18% achieved VO₂-max criteria on the baseline GXT.⁹ Therefore, VO₂-peak may not accurately represent aerobic capacity after stroke.⁷

The oxygen uptake efficiency slope (OUES) and the oxygen consumption rate at the ventilatory threshold (VO₂-VT) are two additional measures of aerobic capacity that can be obtained from a GXT with gas exchange analysis.¹⁰ The OUES represents the rate of increase in oxygen consumption relative to increases in expiratory flow volume during the GXT.¹¹ Therefore, higher OUES values indicate more effective oxygen extraction and utilization.¹¹ VO₂-VT represents the intensity limit of prolonged activity,¹² above which a transition to anaerobic metabolism begins.¹³ Both the OUES and VO₂-VT are primarily influenced by the onset of lactic acidosis, which occurs at submaximal exercise intensities.¹⁰⁻¹² Since these measures are not theoretically dependent on peak exercise intensity and the achievement of VO₂-max,¹⁰ they may be less distorted by motor function.

In other words, OUES and VO2-VT may be more specific measures of aerobic capacity than VO2-peak among persons with stroke. However, this hypothesis has not been previously tested.

One potential concern with VO2-VT is that its measurement requires some rater interpretation and the reliability of VO2-VT determination has not been previously assessed for persons with stroke. Therefore, the aims of this study were to: 1) assess the differential influence of motor function on three measures of aerobic capacity (VO2-peak, OUES and VO2-VT) among persons with stroke; and 2) evaluate the inter-rater reliability of VO2-VT determination in this population. We hypothesized that motor function would be significantly and positively correlated with VO2-peak but would have significantly lower correlations with OUES and VO2-VT. These results would suggest that OUES and VO2-VT are less distorted by motor function than VO2-peak and are thus more specific measures of aerobic capacity after stroke. We also hypothesized that VO2-VT determination would have good inter-rater reliability, as evidenced by an intra-class correlation coefficient above 0.70.

Methods

Study Design

This study involved cross-sectional secondary analyses of data from two laboratories that used comparable methods. In total, data were available from 59 ambulatory participants with chronic stroke who underwent baseline assessments, which included treadmill graded exercise testing (GXT), prior to any intervention. One laboratory used a GXT protocol that primarily progressed treadmill incline (incline GXT, n=33), while the other laboratory used a GXT protocol that primarily progressed treadmill speed (speed GXT, n=26).

For aim 1, these data were used to calculate correlations between measures of motor function and aerobic capacity, after adjusting for potential confounders. The adjusting covariates were selected to isolate the distorting effect of motor function on the aerobic capacity measures. Correlations with motor function were then compared between different measures of aerobic capacity (VO2-peak, OUES and VO2-VT). Aim 2 assessed the inter-rater reliability of VO2-VT determination for persons with stroke. Using standardized methods, three different raters (2 experienced and one novice) made independent VO2-VT determinations using the same GXT data (n=44) and the results were compared between raters.

Settings and Participants

Two studies provided incline GXT data. These studies were approved by the XXX Institutional Review Board. The speed GXT study was approved by the XXX Institutional Review Board. All studies were conducted in rehabilitation research laboratories and all participants provided written informed consent prior to participation.

For the incline GXT studies, inclusion criteria were: 1) age 40 to 85 years; 2) unilateral stroke experienced >6 months prior to enrollment; 3) residual gait impairment; 4) able to walk 10m over ground with no physical assistance; 5) able to walk >3 minutes on the treadmill at .13m/s (0.3mph) with no aerobic exercise contraindications (considered to be

the minimum walking capacity needed to perform a treadmill GXT);^{3,14} 6) stable cardiovascular condition (American Heart Association class B,³ allowing for aerobic capacity <6 metabolic equivalents); 7) able to follow instructions, communicate with investigators and provide informed consent. *Exclusion criteria* were: 1) evidence of significant arrhythmia or myocardial ischemia on treadmill electrocardiographic (ECG) stress test;³ 2) hospitalization for cardiac or pulmonary disease within the past 3 months; 3) pacemaker or implanted defibrillator; 4) lower extremity claudication; 5) severe lower extremity spasticity (Ashworth 3);¹⁵ 6) lower extremity weight bearing pain >4/10 on a visual analogue scale.

For the speed GXT study, *inclusion criteria* were: 1) age 21 to 85 years; 2) chronic stroke (>6 months post stroke, first/single lesion); 3) ambulatory without the assistance of another person but with residual gait deficit; 4) able to walk for 5 minutes at their self-selected speed on the treadmill; 5) resting heart rate between 40-100 beats per minute; 6) resting blood pressure not exceeding 170/90; 7) average steps per day <10,000; 8) able to walk outside the home prior to stroke. *Exclusion criteria* were: 1) evidence of cerebellar stroke on magnetic resonance imaging; 2) inability to communicate with investigators; 3) unexplained dizziness in the last 3 months; 4) cardiac event or surgery in the last 3 months; 5) pain that limits walking; 6) other diagnosed neurological disease or prior stroke; 7) lower limb botulinum toxin within the last 4 months; 8) participation in current physical therapy.

Clinical Examination

Both laboratories used similar baseline assessments involving a medical history, medical record review, physical assessments and physical performance tests, including a treadmill ECG stress test. Available motor function variables were comfortable gait speed (CGS), measured with the 10 meter walk test,¹⁶ and the lower extremity motor portion of the Fugl-Meyer stroke assessment (LEFM).¹⁷ The LEFM includes 17 items assessing reflexes, movement synergies and coordination on a scale from 0 to 2, yielding a total summed score from 0 to 34, where higher values represent less motor impairment.¹⁷ Both CGS and the LEFM are reliable and valid for persons with stroke.^{18,19} Other variables used for these analyses included age, sex, years post stroke, body mass index (BMI), depression and physical activity. Depression diagnosis (yes/no) was determined from the medical history. Physical activity was measured using a StepWatch Activity Monitor attached to the non-paretic ankle for 3 days and was quantified by the average number of steps per day.²⁰⁻²³ The incline GXT laboratory only measured physical activity in one of two studies that were pooled for this analysis. Therefore, steps per day data were only available for 17 out of 33 incline GXT participants.

Graded Exercise Testing (GXT) Protocols

Both laboratories performed baseline treadmill GXTs to assess aerobic capacity, using the same model of metabolic cart for respiratory gas exchange analysis (Parvomedics TrueOne 2400²⁴). The metabolic carts were calibrated in accordance with manufacturer guidelines. One laboratory used a protocol that primarily progressed incline, while the other laboratory used a protocol that primarily progressed speed.

Incline GXT Protocol—Prior to the GXT, a treadmill screening test was performed to acclimate the participant to treadmill walking and select a challenging but sustainable speed for the GXT.¹⁴ During the GXT, speed was held constant at the predetermined value. Incline was started at 0% and was increased by 2-4% every 2 minutes²⁵ until volitional fatigue, severe gait instability or a cardiovascular safety limit.^{3,26}

Speed GXT Protocol—Prior to the GXT, a treadmill screening test was performed to acclimate the participant to treadmill walking and determine the self-selected and fastest safe treadmill speeds. During the GXT, incline was started at 0% and speed was started at or 0.2 mph below the participant's self-selected treadmill walking speed. Speed was increased by 0.1 mph (self-selected speed <1.0 m/s) or 0.2 mph (self-selected speed ≥ 1.0 m/s) every 2 minutes until volitional fatigue, severe gait instability, a cardiovascular safety limit^{3,26} or the participant achieved 85% of age-predicted HR_{max} or a rating of perceived exertion ≥ 19 out of 20. If the participant achieved their fastest walking speed without reaching one of these endpoints, incline was increased by 2% every 2 minutes until an endpoint was reached.

Aerobic Capacity Determination

Aerobic capacity measures obtained for each participant included VO₂-peak, OUES and VO₂-VT.

- VO₂-peak was calculated as the highest 20 second average oxygen consumption rate recorded during the GXT (Figure 1, top left panel).¹²
- Oxygen uptake efficiency slope (OUES) was calculated using the equation: VO₂ (mL/min) = OUES * log₁₀ VE (L/min) + intercept; where OUES is the slope of the regression line of VO₂ vs. log transformed expiratory flow volume (Figure 1, bottom left panel).^{10,11}
- VO₂-VT was determined using a combination of the V-slope and ventilatory equivalents methods (Figure 1, right panels).^{10,13} Specific standardized methods used for VO₂-VT determination are shown in the appendix.

Inter-rater Reliability Testing for VO₂-VT Determination (Aim 2)

Three raters independently made VO₂-VT determinations for all available tests. Two of the raters each had over 3 years of experience in VO₂ determination (XX and XX) and one had no previous experience (XX). A one-hour standardization session was conducted prior to rating. Independent VO₂-VT determinations were then made using the methods described above and the software included with the metabolic cart system. For one of the two incline GXT studies that were pooled for this analysis, data were not available in the file type of the metabolic cart software. Therefore, data for VO₂-VT reliability testing were only available for 17 out of 33 incline GXT participants. One speed GXT participant who could not be included in the aim 1 analysis due to a missing covariate was able to be included in the aim 2 analysis. This raised the speed GXT sample size to 27 and the combined sample size to 44 for this analysis.

Statistical Analysis

Participant characteristics were compared between the incline GXT and speed GXT subsamples, using independent t-tests for continuous variables and chi-squared tests for dichotomous variables. Bivariate (unadjusted) Pearson correlations were then obtained for all pairwise comparisons between variables. Absolute values of correlation coefficients were interpreted as follows: 0.01-0.25=very low/very weak; 0.26-0.49=low/weak; 0.50-0.69=moderate; 0.70-0.89=high; 0.90-1.00=very high.⁸

For the aim 1 analysis, partial (adjusted) correlations were calculated between each motor function measure (CGS, LEFM) and each measure of aerobic capacity (VO₂-peak, OUES and VO₂-VT). A directed acyclic graph approach²⁷ was used to determine which variables would be appropriate to use to adjust for the effects of true aerobic capacity and aid in isolating the distorting effect of motor function on the aerobic capacity measures. Based on the literature, we identified the following potential common causes of both motor dysfunction (lower CGS) and lower aerobic capacity measurement: greater stroke severity,^{20,28-30} increased age,^{3,31} female sex,^{3,31} higher BMI,^{3,32,33} depression^{34,35} and lower physical activity history.^{1,3,20} Hypothesized causal relationships were graphed with unidirectional arrows (Figure 2). To obtain a minimally biased estimate of the distorting association between motor function and each aerobic capacity measurement, all other pathways indirectly connecting these two variables had to be blocked by covariate adjustment.²⁷ This approach indicated that age, sex, BMI, depression and physical activity history (steps per day) should be included as covariates in the partial correlations.

The adjusted correlations between motor function and aerobic capacity were then compared between the different measures of aerobic capacity (VO₂-peak, OUES and VO₂-VT), using the test of Kleinbaum et al for the equality of two paired correlations.³⁶ This analysis was performed on the full dataset and separately for the incline GXT and speed GXT data subsets. GXT protocol was also included as a covariate in the full dataset analysis. With a two-sided test and a significance level of 0.05, a sample size of 59 provides 80% power to detect a Pearson correlation as small as 0.36. A previous meta-analysis found a correlation of 0.42 between VO₂-peak and CGS.⁸

Since steps per day data were only available for 17 out of 33 incline GXT participants, this covariate was not included in the primary analysis so that the full available sample could be used. Instead, a sensitivity analysis was performed to assess for residual confounding due to lack of adjustment for steps per day. This analysis used the subset of participants with full available data (43 out of 59) and compared the partially adjusted correlation coefficients from the primary analysis (not including steps per day) to the fully adjusted correlation coefficients (including steps per day). A difference >10% between the partially and fully adjusted correlation coefficients would have indicated the presence of residual confounding.³⁶

For the aim 2 analysis, inter-rater reliability of VT determination was assessed by comparing mean VO₂-VT determinations between raters with analysis of variance (ANOVA). In addition, intra-class correlation coefficients (ICC 2,1) were calculated between all three

raters and for each pairwise rater comparison. R version 3.0.0³⁷ and the psych package were used for the ICC analyses. SAS version 9.4 was used for all other analyses.

Results

Participant characteristics are shown in table 1. Age, sex, BMI, comfortable gait speed and OUES were similar between the incline GXT and speed GXT samples, while steps per day, LEFM and VO2-VT were significantly different and stroke chronicity, depression and VO2-peak were borderline significant. An unadjusted correlation matrix for the full combined dataset (n=59) is shown in table A (Supplemental Online Material).

Adjusted Correlations Between Motor Function and Aerobic Capacity Variables (Aim 1)

Table 2 shows the correlations between aerobic fitness and motor function variables after adjusting for all identified potential confounders except physical activity history (i.e. GXT protocol, age, sex, BMI and depression). In the full data set (n=59), CGS was moderately correlated with VO2-peak ($r=0.52$, $p<0.0001$) and weakly correlated with OUES ($r=0.41$, $p=0.002$) and VO2-VT ($r=0.37$, $p=0.01$). Likewise, the LEFM was weakly correlated with VO2-peak ($r=0.26$, $p=0.055$) and very weakly correlated with OUES ($r=0.19$, $p=0.17$) and VO2-VT ($r=0.14$, $p=0.31$). Compared to VO2-peak, VO2-VT was significantly less correlated with CGS (r difference = -0.16 , $p=0.02$). None of the other comparisons between correlation coefficients were statistically significant (Table 3).

Compared to the full data set, the overall results were the same in the incline GXT data subset, but there were some differences in the speed GXT subset (Table 2). The speed GXT data showed a moderate (rather than low) correlation between VO2-VT and CGS ($r=0.51$, $p=0.01$), resulting in a non-significant difference in the CGS correlation between VO2-VT and VO2-peak ($p=0.69$). On the other hand, the speed GXT data showed a higher and significant correlation between VO2-peak and the LEFM ($r=0.43$, $p=0.048$), resulting in a difference nearing statistical significance for the LEFM correlation comparison between VO2-VT and VO2-peak (r difference= 0.22 , $p=0.06$).

Physical activity history was identified as a potential confounder but could not be adjusted for in the above correlations, because steps per day data were only available for a subset of participants (43 out of 59). Therefore, a sensitivity analysis was conducted using this subset to test for residual confounding due to the lack of adjustment for physical activity history (Table B, Supplemental Online Material). For VO2-peak and VO2-VT, the differences between the partially adjusted correlation coefficients (not including steps per day) and the fully adjusted correlation coefficients (including steps per day) ranged from 0.00 to 0.04 (0 to 9.5%). Therefore, for these variables, there was no evidence of residual confounding by not adjusting for steps per day. For OUES, the differences between partially and fully adjusted correlation coefficients ranged from 0.03 to 0.09 (7 to 20%), indicating the presence of residual confounding. However, adjusting for steps per day did not change the interpretation of the correlations between OUES and the motor function variables. In addition, there were still no statistically significant differences in the motor function correlations between OUES and the other aerobic capacity measures (r differences = -0.08 to 0.18 , $p = 0.17$ to 0.84).

Inter-rater Reliability of Ventilatory Threshold (VT) Determination (Aim 2)

In the subset of participants with available GXT data in the file type of the metabolic cart software (n=44), mean (SD) VO₂-VT determinations were 10.5 (2.8) for rater A (experienced), 10.7 (2.9) for rater B (experienced) and 10.6 (2.6) for rater C (novice). Using ANOVA, no statistically significant differences were found in mean VO₂-VT determinations between raters (p=.94). The overall ICC for the full data set comparing all 3 raters was 0.93 [95% CI: 0.89 to 0.96]. The ICCs for the incline and speed GXT data subsets and the pairwise comparisons between raters ranged from 0.84 to 0.97 (Table 3).

Discussion

In this cross sectional analysis of 59 persons with chronic stroke, VO₂-peak, OUES and VO₂-VT were all significantly correlated with walking speed (CGS), even after adjusting for other factors that could influence this correlation. This suggests that aerobic capacity measurement is distorted by motor dysfunction after stroke, rather than representing a pure assessment of aerobic capacity. Compared to VO₂-peak, VO₂-VT was significantly less correlated with CGS, suggesting that VO₂-VT may be a more specific measure of aerobic capacity in this population.

Compared to CGS, the LEFM showed similar relative differences in correlations between the aerobic capacity measures. However, the LEFM correlations were lower than the CGS correlations and were non-significant. This discrepancy between CGS and the LEFM is likely related to task-specificity. Since this study involved walking GXT data, CGS is probably a better measure to assess the influence of motor dysfunction on the aerobic capacity measures. This study also found that standardized methods of VO₂-VT determination had good inter-rater reliability for both data subsets, even between novice and experienced raters. These findings have important implications for stroke rehabilitation research and practice.

The vast majority of previous stroke studies have used VO₂-peak to represent aerobic capacity.^{e.g.1,2,4,8} These studies have suggested that aerobic deconditioning is severe enough to drastically limit performance of daily activities for most persons with stroke.^{1,2,4} However, given the results of the current study, it is possible that the low VO₂-peak levels previously observed are partially attributable to motor dysfunction, rather than solely aerobic deconditioning. It is important to note that there are converging lines of evidence indicating that aerobic deconditioning is common after stroke and can negatively impact recovery. For example, persons with stroke have been found to exhibit high rates of cardiovascular comorbidity, low levels of daily physical activity, skeletal muscle atrophy, elevated inflammatory markers and abnormal glucose regulation.⁵ However, future studies are now needed to quantify the true magnitude of aerobic deconditioning after stroke so that interventions can be appropriately prioritized. In addition, studies are needed to assess the efficacy of different exercise parameters for specifically improving aerobic capacity after stroke.

Similar to the current study, a previous meta-analysis of 13 studies (n=454) found an unadjusted correlation between VO₂-peak and CGS of 0.42 [95% credibility interval:

0.31-0.54].⁸ The authors suggested that these correlations provide evidence that walking speed can be improved by increasing aerobic capacity.⁸ However, the current study suggests a different interpretation of these findings based on an alternative causal model (Figure 2). Instead of proposing that decreased aerobic capacity results in lower walking speed, our causal model shows how lower walking speed could result in a lower VO₂-peak measurement, without necessarily lowering aerobic capacity (solid arrow in Figure 2). Our data seem to be consistent with this model, since adjusting for factors that are associated with the construct of aerobic capacity (i.e. age, sex, BMI, depression and physical activity), did not eliminate the association between motor function and VO₂-peak. However, such adjustment also did not eliminate the motor function associations with OUES and VO₂-VT. Therefore, it is possible that OUES and VO₂-VT are also partially distorted by motor function or that there was incomplete control of confounding. Cross-sectional correlation studies such as this cannot establish causation, so different study designs will be needed to resolve the dilemma of which causal model is more accurate.

Aside from being cross-sectional, the primary limitation to this study is that there is currently no gold standard measure for aerobic capacity for persons with stroke. This made it difficult to isolate the distorting effect of motor function on the aerobic capacity measures. Without being able to measure 'true' aerobic capacity, we had to indirectly control for it by adjusting for covariates that can alter it (Figure 2). It is possible that not all relevant covariates were included or that some covariates were measured with error, and this could have influenced the results. Future stroke GXT studies may benefit from assessment of cardiac output and peripheral oxygen extraction^{38,39} to better elucidate the effects of motor function on different aerobic capacity measures.

Another potential study limitation was that data were combined across two studies with slightly different geographic locations, eligibility criteria, and GXT protocols. Although we adjusted for potential confounding variables when combining results across these studies, it is still possible that between-study differences may have influenced these results in unknown ways. However, a strength to this approach is that it allowed us to assess the consistency of these findings across two cohorts of persons with stroke and two GXT protocols.

For example, the difference in CGS correlations between VO₂-peak and VO₂-VT was not consistent between study data subsets. In the speed GXT subset, VO₂-peak and VO₂-VT showed similar correlations with CGS because the correlation between VO₂-VT and CGS was higher than that observed in the incline GXT subset. These divergent findings between data subsets may relate to differences between the GXT protocols. Unlike the incline GXT protocol, the speed GXT protocol was largely based on the participant's gait speed. Therefore, it seems likely that the correlation between VO₂-VT and CGS was artificially inflated in the speed GXT subset. In contrast, the LEFM (which does not measure gait) showed the expected pattern of correlations in this subset. There was a significant correlation between the LEFM and VO₂-peak, a non-significant correlation between the LEFM and VO₂-VT and a nearly significant difference between these two correlations (r difference=0.22, p =0.06). Therefore, both GXT protocols seemed to indicate that VO₂-VT was less distorted by motor function than VO₂-peak.

The results for the OUES were less clear. OUES had the highest bivariate correlation with steps per day ($r=0.41$, $p=0.01$) and showed a trend toward lower motor function correlations than VO2-peak. However, none of these differences reached statistical significance. It is important to note that the paired correlation comparison test has lower power when the two variables being compared are not well correlated.³⁶ In this case, OUES and VO2-peak were only moderately correlated ($r=0.52$), making it more difficult to find significant differences. In addition, the sensitivity analysis found residual confounding in the OUES correlations when not adjusting for steps per day. Adjusting for steps per day in the subset of participants with available data generally decreased the correlation between OUES and the motor function variables. Therefore, it is possible that with a larger sample size when including all potential confounders, OUES may show significant differences from VO2-peak. However, it has been previously shown in adolescents that OUES may be sensitive to the aerobic intensity achieved during the GXT, such that submaximal intensities artificially decrease OUES and decrease the correlation between OUES and VO2-peak.⁴⁰ Since motor dysfunction makes it more difficult to reach maximum aerobic capacity on a GXT, it is possible that OUES, like VO2-peak, may be distorted post-stroke.

Conclusions

The results of this cross-sectional study indicate that VO2-peak may be distorted by motor dysfunction after stroke, resulting in artificially low measurement of aerobic capacity. This distorting effect appeared to be less pronounced for VO2-VT and possibly OUES, suggesting that these measures obtained at submaximal exercise intensities may provide more specific assessment of aerobic capacity in this population. Further studies are needed to confirm these results and to reevaluate the independent and combined importance of motor function and aerobic capacity in stroke recovery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Standardized Method of VO2-VT Determination

- Start with the V-slope graph (Fig 1, 3rd panel) & 20 second averaging
 - If there are multiple CO₂ data points at each VO₂ level, increase the averaging duration to clarify
 - If there are few data points (e.g. <15) with large gaps between points, decrease the averaging duration to clarify

- Starting at the bottom left corner of the graph, begin mentally drawing a line of best fit. The VT is the last point on this line before the slope increases.
- Use the ventilatory equivalents graph (Fig 1, bottom panel) to confirm. The VT is the lowest point on the VE/VO₂ line, just before its slope starts increasing more than the VE/VCO₂ line.
- For consistency, select the final VT point from the V-Slope graph with 20 second averaging

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Figure 1. Example VO2-peak, oxygen uptake efficiency slope (OUES) and ventilatory threshold (VT) determinations for one graded exercise test (GXT)

VO2-peak (top left panel) is the highest oxygen consumption rate recorded during the test. In this example, VO2-peak is 15.7 mL/kg/min. OUES (bottom left panel) is the slope of the linear regression line of VO2 vs. $\log_{10}$ VE (expiratory flow rate). In this example, the OUES is 2,194 (mL/min)/(L/min). VT is determined by the V-slope graph (top right panel) and confirmed by the ventilatory equivalents graph (bottom right panel). In the V-slope graph, the VT is the last point before the slope increases. In the ventilatory equivalents graph, the VT is the lowest point on the VE/VO2 line, just before its slope starts increasing more than the VE/VCO2 line. In this example, the identified VT points on each graph correspond to the same data point (VO2-VT = 1121 mL/min / 105 kg participant weight = 10.7 mL/kg/min). This point is also shown on the VO2-peak graph (top left panel).

VCO2, carbon dioxide expiration rate; VO2, oxygen consumption rate.

Figure 2. Directed acyclic graph of the potential confounding factors for the association between motor function and exercise testing measures

Arrows represent hypothesized causal relationships. To obtain an unbiased estimate of the associations between current motor function and exercise testing measures (solid arrow), all other pathways indirectly connecting these solid boxes must be blocked by covariate adjustment. This graph indicates that the following covariates should be included: age, sex, BMI, depression and physical activity history.

BMI, body mass index; VO₂-peak, oxygen consumption rate at peak exercise; OUES, oxygen uptake efficiency slope; CGS, comfortable gait speed; LEFM, lower extremity Fugl-Meyer scale.

Table 1
Participant Characteristics

	Incline GXT (n=33)	Speed GXT (n=26)	P value	Full data set (n=59)
Age, years	59.6 ± 7.9	58.5 ± 10.2	0.65	59.1 ± 8.9
Male sex	19 (58%)	15 (58%)	0.99	34 (58%)
Years post stroke	5.3 ± 3.9	3.5 ± 3.1	0.07	4.5 ± 3.7
Body mass index, kg/m ²	28.5 ± 5.5	30.4 ± 6.8	0.23	29.3 ± 6.1
Depression diagnosis	14 (42%)	5 (19%)	0.058	19 (32%)
Physical activity, steps/day	3,302 ± 1,724 *	4,931 ± 2,627	0.03	4,287 ± 2,427 *
Comfortable gait speed, m/s	0.63 ± 0.30	0.63 ± 0.36	0.99	0.63 ± 0.33
LEFM score (0-34)	25.0 ± 4.8	17.6 ± 4.8	<0.01	21.8 ± 6.0
VO ₂ -peak, mL/kg/min	17.0 ± 4.1	14.9 ± 4.2	0.07	16.1 ± 4.2
VO ₂ -VT, mL/kg/min	11.2 ± 3.1	9.8 ± 2.1	0.04	10.6 ± 2.8
OUES, (mL/min)/(L/min)	1,688 ± 306	1,842 ± 437	0.12	1,756 ± 374

Data are presented as mean ± SD or n (%). P values are from independent t-tests (continuous variables) or chi-squared tests (dichotomous variables) comparing the incline GXT and speed GXT data subsets.

* For incline GXT subset, physical activity data were only available for 17/33 participants

GXT, graded exercise test; LEFM, lower extremity Fugl-Meyer scale; VO₂-peak, oxygen consumption rate at peak exercise; VO₂-VT oxygen consumption rate at the ventilatory threshold; OUES oxygen uptake efficiency slope

Table 2

Adjusted correlations between aerobic fitness and motor function variables and correlation comparisons between different aerobic measures

		Comfortable gait speed (CGS)					
		r_1 VO2-peak, CGS	r_2 OUES, CGS	r_3 VO2-VT, CGS	$r_1 - r_2$ VO2-peak – OUES	$r_2 - r_3$ OUES – VO2-VT	$r_1 - r_3$ VO2-peak – VO2-VT
Full data set (n=59)		0.52 (<.01)	0.41 (<.01)	0.37 (.01)	0.11 (.32)	0.05 (.70)	0.16 (.02)
Incline GXT (n=33)		0.56 (<.01)	0.44 (.02)	0.32 (.09)	0.11 (.38)	0.13 (.42)	0.24 (<.01)
Speed GXT (n=26)		0.55 (.01)	0.48 (.02)	0.51 (.01)	0.08 (.60)	-0.03 (.83)	0.04 (.69)
		Lower extremity Fugl-Meyer scale (LEFM)					
		r_1 VO2-peak, LEFM	r_2 OUES, LEFM	r_3 VO2-VT, LEFM	$r_1 - r_2$ VO2-peak – OUES	$r_2 - r_3$ OUES – VO2-VT	$r_1 - r_3$ VO2-peak – VO2-VT
Full data set (n=59)		0.26 (.055)	0.19 (.17)	0.14 (.31)	0.07 (.56)	0.05 (.72)	0.12 (.09)
Incline GXT (n=33)		0.28 (.15)	0.07 (0.72)	0.16 (.42)	0.21 (.17)	-0.09 (.60)	0.12 (.18)
Speed GXT (n=26)		0.43 (.048)	0.34 (.12)	0.21 (.35)	0.09 (.59)	0.13 (.48)	0.22 (.06)

Data are correlation coefficients (p values), adjusted for GXT protocol (full data set only), age, gender, BMI and depression. GXT, graded exercise test; VO2-peak, oxygen consumption rate at peak exercise; OUES, oxygen uptake efficiency slope; VO2-VT, oxygen consumption rate at ventilatory threshold

Table 3
Inter-rater reliability of VO2-VT determination

	All 3 Raters	Raters 1 & 2*	Raters 1 & 3	Raters 2 & 3
Full data set (n=44)	0.93 [0.89-0.96]	0.95 [0.91-0.97]	0.93 [0.87-0.96]	0.92 [0.85-0.95]
Incline GXT (n=17)	0.95 [0.90-0.98]	0.95 [0.86-0.98]	0.97 [0.92-0.99]	0.94 [0.84-0.98]
Speed GXT (n=27)	0.88 [0.78-0.94]	0.94 [0.86-0.97]	0.84 [0.68-0.92]	0.85 [0.70-0.93]

Data are intra-class correlation coefficients (ICC 2,1) [95% confidence intervals]. VO2-VT, oxygen consumption rate at the ventilatory threshold. GXT, graded exercise test

*
raters experienced in VO2-VT determination