Cardiac Reserve and Pulmonary Gas Exchange Kinetics in Patients With Stroke

Corey R. Tomczak, MSc; Anwar Jelani, MD; Robert G. Haennel, PhD; Mark J. Haykowsky, PhD; Robert Welsh, MD; Patricia J. Manns, PhD

Background and Purpose—Cardiovascular and pulmonary factors contributing to impaired peak oxygen uptake (VO₂) in patients with stroke (SP) are not well known. We assessed cardiovascular function, pulmonary gas exchange, and ventilation in SP and healthy age, gender, and activity-matched control subjects.

Methods—Ten hemiparetic SP and 10 control subjects were enrolled. Subjects completed cycle ergometry testing to assess peak and reserve VO₂, carbon dioxide production, ventilation (tidal volume; breathing frequency; minute ventilation), and cardiac output. VO₂, carbon dioxide production, and minute ventilation were measured throughout peak exercise recovery (off-kinetics) and at exercise onset (on-kinetics) along with heart rate during low-level exercise.

Results—Peak VO₂ was 43% lower (P<0.001) in SP secondary to reduced peak and reserve cardiac output and minute ventilation. The impaired cardiac output reserve (P<0.001) was due to a 34% lower heart rate reserve (P=0.001). The impaired minute ventilation reserve (P=0.013) was due to a 41% lower tidal volume reserve (P=0.009). Stroke volume and breathing frequency reserve were preserved. VO₂ off-kinetics were 29% slower in SP (P<0.001) and related to peak VO₂ (R=−0.72, P<0.001) and peak cardiac output (R=−0.75, P<0.001) for the study group. Additionally, carbon dioxide production (P=0.016) and minute ventilation (P=0.023) off-kinetics were prolonged in SP. VO₂ on-kinetics were 29% slower (P=0.031) during low-level exercise in SP.

Conclusions—The impaired peak VO₂ in SP is secondary to a decline in peak and reserve cardiac output and ventilation. Prolonged VO₂ kinetics in SP are associated in part with deconditioning and may be mediated by reduced O₂ availability and/or the rate of muscle O₂ use. (Stroke. 2008;39:3102-3106.)

Key Words: cardiac output ■ exercise ■ oxygen uptake kinetics ■ stroke

The cardiopulmonary factors that contribute to the abnormal oxygen uptake (VO₂) in patients with stroke (SP) are not well known. Although left ventricular function may be compromised in acute SP,4 cardiac function during exercise has not been evaluated. Circulatory impairments adversely impact peak VO₂ in addition to the recovery of VO₂ after exercise,2 yet this relationship has not been established in SP. Additionally, it is not known whether impairments in the rate of VO₂ readjustment are present during low-level exercise comparable to activities of daily living in SP.

We tested the hypotheses that (1) peak and reserve VO₂ and cardiac output (Q) would be lower in SP; (2) pulmonary gas exchange and ventilation off-kinetics would be slower in SP; (3) slower VO₂ off-kinetics would be associated with a lower peak VO₂ and Q; and (4) VO₂ on-kinetics would be prolonged during low-level exercise in SP compared with healthy control subjects.

Materials and Methods
Ten hemiparetic SP and 10 healthy control subjects were enrolled (Table 1). This investigation was approved by the research ethics board at the University of Alberta and participants provided written and informed consent.

Testing was completed on a custom-modified recumbent cycle ergometer to assess peak and reserve (peak—rest) VO₂, carbon dioxide production (VCO₂), ventilation (tidal volume, VT; breathing frequency; minute ventilation, VE; Parvomedics, Salt Lake City, Utah), and Q (Minnesota Impedance Cardiograph, model 304B; Surcom, Minneapolis, Minn.). VO₂, VCO₂, and VE off-kinetics were determined. On a separate day, subjects completed 3 square-wave exercise protocols separated by 25 minutes to assess VO₂, VCO₂, VE, and heart rate (HR) on-kinetics. A 5-minute resting baseline was followed by 5 minutes of cycling at a power output approximating 80% of the ventilatory threshold.

Breath-by-breath off-kinetics data were averaged into 10-s bins for curve fitting and on-kinetics data from the 3 repeats were interpolated to 1-s intervals, time-aligned, averaged to yield a single response, and averaged into 5-s bins. VO₂, VCO₂, and VE off-kinetics (Eq 1) and on-kinetics (Eq 2) were determined using the following equations:

\[ Y_{\text{on}} = Y_{\text{on}(-)} - A [1 - e^{-(HR - TD)/\gamma}] \]

\[ Y_{\text{off}} = Y_{\text{off}(-)} + A [1 - e^{-(HR - TD)/\gamma}] \]
where $Y$ is the parameter at any time ($t$), $peak$ is the greatest 30-s value of $Y$, and $rest$ is the value of $Y$ over 1 minute before exercise onset, $A$ is the amplitude change in $Y$, $/H_{9270}$ is the time to reach a 63% change in $Y$, and $TD$ is the time delay before the exponential change in $Y$.

Phase II $\dot{V}O_2$, $\dot{V}CO_2$, and VE on-kinetics were determined and HR on-kinetics were measured from exercise onset. The best curve fit was defined by minimization of the residual sum of squares (Origin 7.5; OriginLab Corp, Northampton, Mass).

Analysis of variance was used for between-group comparisons and correlation regression to determine variable relationships. Data are mean±SEM and $P<0.05$ was significant.

### Results

Peak $\dot{V}O_2$, $\dot{V}CO_2$, VE, HR, stroke volume (SV), $Q$, systemic vascular resistance, and power output were lower in SP

### Table 1. Demographic and Clinical Features of the Stroke and Control Group

<table>
<thead>
<tr>
<th></th>
<th>Stroke (n=10)</th>
<th>Control Subjects (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years*</td>
<td>54±3</td>
<td>54±3</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>4:6</td>
<td>4:6</td>
</tr>
<tr>
<td>Height, cm*</td>
<td>170±3</td>
<td>168±2</td>
</tr>
<tr>
<td>Mass, kg*</td>
<td>82.4±5.5</td>
<td>74.3±3.3</td>
</tr>
<tr>
<td>Body mass index, kg/m²**</td>
<td>29±2</td>
<td>26±1</td>
</tr>
<tr>
<td>Brain lesion side, left:right</td>
<td>6:4</td>
<td>...</td>
</tr>
<tr>
<td>Stroke type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>5</td>
<td>...</td>
</tr>
<tr>
<td>Ischemic</td>
<td>5</td>
<td>...</td>
</tr>
<tr>
<td>Time since stroke, years*</td>
<td>7.5±2.6</td>
<td>...</td>
</tr>
<tr>
<td>Range, years</td>
<td>0.8–29.0</td>
<td>...</td>
</tr>
<tr>
<td>Gait speed, m/min*</td>
<td>43±5</td>
<td>...</td>
</tr>
<tr>
<td>Range, m/min</td>
<td>21–72</td>
<td>...</td>
</tr>
<tr>
<td>Activity level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 days/week, n (%)</td>
<td>6 (60)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>2 days/week, n (%)</td>
<td>3 (30)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>1 day/week, n (%)</td>
<td>1 (10)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Hypertension/hypertensive exercise response, n (%)</td>
<td>6 (60)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>1 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, n (%)</td>
<td>1 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>5 (50)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Prior cardiac arrest (stroke-related), n (%)</td>
<td>1 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Former smoker, n (%)</td>
<td>5 (50)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor, n (%)</td>
<td>4 (40)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Angiotensin II receptor blocker, n (%)</td>
<td>4 (40)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Beta-blocker, n (%)†</td>
<td>3 (30)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Calcium channel blocker, n (%)</td>
<td>1 (10)</td>
<td>0 (0)</td>
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<tr>
<td>Antidiuretic, n (%)</td>
<td>1 (10)</td>
<td>0 (0)</td>
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<tr>
<td>Thiazide diuretic, n (%)</td>
<td>4 (40)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Antiplatelet, n (%)</td>
<td>4 (40)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Statin and/or antihyperlipidemic, n (%)</td>
<td>5 (50)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nitroglycerin, n (%)</td>
<td>1 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bronchodilator, n (%)</td>
<td>1 (10)</td>
<td>0 (0)</td>
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<tr>
<td>Anticonvulsant, n (%)</td>
<td>1 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diabetic-related medication, n (%)</td>
<td>1 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ankle–foot orthosis, n (%)</td>
<td>6 (60)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Walking aid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None, n (%)</td>
<td>1 (10)</td>
<td>...</td>
</tr>
<tr>
<td>Single-point cane, n (%)</td>
<td>6 (60)</td>
<td>...</td>
</tr>
<tr>
<td>Quad cane, n (%)</td>
<td>3 (30)</td>
<td>...</td>
</tr>
</tbody>
</table>

*Data are mean±SEM. Remaining data are n (%).
†Withheld for exercise testing.
Table 2. Pulmonary Gas Exchange, Ventilation, and Cardiovascular Parameters

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Peak Exercise</th>
<th>Reserve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stroke</td>
<td>Control</td>
<td>P Value</td>
</tr>
<tr>
<td>Power output, W</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>V\textsubscript{O}_2, mL/kg/min</td>
<td>3.2±0.3</td>
<td>3.7±0.2</td>
<td>0.149</td>
</tr>
<tr>
<td>V\textsubscript{O}_2, L/min</td>
<td>0.25±0.02</td>
<td>0.27±0.02</td>
<td>0.460</td>
</tr>
<tr>
<td>V\textsubscript{CO}_2, mL/kg/min</td>
<td>2.8±0.2</td>
<td>3.2±0.2</td>
<td>0.195</td>
</tr>
<tr>
<td>VE, L/min</td>
<td>9.6±0.6</td>
<td>9.5±0.7</td>
<td>0.934</td>
</tr>
<tr>
<td>Breathing frequency (breaths/min)</td>
<td>18±2</td>
<td>15±2</td>
<td>0.208</td>
</tr>
<tr>
<td>VT (L)</td>
<td>0.55±0.05</td>
<td>0.66±0.05</td>
<td>0.147</td>
</tr>
<tr>
<td>V\textsubscript{CO}/V\textsubscript{O}_2</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>74±3</td>
<td>67±2</td>
<td>0.098</td>
</tr>
<tr>
<td>Stroke volume, mL/beat</td>
<td>59±3</td>
<td>69±2</td>
<td>0.008</td>
</tr>
<tr>
<td>Cardiac output, L/min*</td>
<td>4.4±0.4</td>
<td>4.6±0.2</td>
<td>0.556</td>
</tr>
<tr>
<td>a-V\textsubscript{O}_2\textsubscript{aS}, mL/100 mL</td>
<td>6±1</td>
<td>6±0.5</td>
<td>0.629</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>123±10</td>
<td>123±4</td>
<td>0.972</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>78±4</td>
<td>76±3</td>
<td>0.751</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>95±5</td>
<td>92±3</td>
<td>0.870</td>
</tr>
<tr>
<td>SVR, dynes/cm\textsuperscript{5}</td>
<td>1824±138</td>
<td>1607±82</td>
<td>0.172</td>
</tr>
</tbody>
</table>

*Data not obtained in 3 stroke subjects because of technical difficulties. Reserve values were calculated as peak exercise—rest. Data are mean±SEM. a-V\textsubscript{O}_2\textsubscript{aS} indicates systemic arterial–venous O\textsubscript{2} difference.

Discussions

The major new findings of this investigation are that (1) the reduction in peak and reserve V\textsubscript{O}_2 in SP is secondary to an impaired peak and reserve Q and VE; (2) prolonged V\textsubscript{O}_2 off-kinetics in SP is related to a reduced peak V\textsubscript{O}_2 and Q; and (3) SP have slower V\textsubscript{O}_2 on-kinetics during low-level exercise.

We demonstrate that impaired V\textsubscript{O}_2 in SP is secondary to a lower peak and reserve Q. The impaired Q reserve was secondary to an impaired HR reserve, because SV reserve was not different between groups (Table 2). Our finding of a similar SV reserve despite a higher systemic vascular resistance in SP (Table 2) is likely due to an enhanced preload or contractile reserve. This is plausible given that peak exercise end systolic volume likely increased secondary to an increased afterload. Additionally, systolic peak velocity is inversely related to afterload. Thus, the lower peak and reserve HR (Table 2) in our SP would lead to a greater diastolic filling time, preserving preload and SV reserve.

Peak and reserve VE was lower in SP secondary to an impaired peak and reserve VT, because peak and reserve breathing frequency were not different between groups (Table 2). Electromyographic activity is reduced in ventilatory muscles contralateral to the brain lesion side in SP and may be exacerbated during increases in VT, thus contributing to an overall lower peak and reserve VT.

V\textsubscript{O}_2 remained elevated throughout recovery in SP (Figure A), reflecting a slower rate of skeletal muscle energy restoration. This is determined in part by the oxidative capacity and maximal rate of oxidative adenosine triphosphate synthesis of skeletal muscle, which may be mediated by aerobic fitness and the availability of O\textsubscript{2} for phosphocreatine regeneration. Indeed, a lower peak V\textsubscript{O}_2 was associated with prolonged V\textsubscript{O}_2 off-kinetics in our SP. Consistent with the hypothesis that O\textsubscript{2} availability may be rate-limiting for V\textsubscript{O}_2 recovery, peak Q and V\textsubscript{O}_2 off-kinetics were well correlated.

V\textsubscript{CO}_2 and VE off-kinetics were prolonged in SP (Figure A). Prolonged V\textsubscript{CO}_2 kinetics are explained by a greater CO\textsubscript{2} tension in the skeletal muscle secondary to buffering of exercise-induced lactate. This is consistent with the ventilatory threshold occurring at a lower exercise intensity in SP, suggesting a more immediate reliance on anaerobic glycolysis. The lower Q may also have exacerbated the delay in recovery V\textsubscript{CO}_2. Resulting CO\textsubscript{2} levels likely contributed to the
high VE, which is consistent with the well-correlated V˙CO₂ and V˙E off-kinetics.

V˙O₂ on-kinetics were slower in SP (Figure B), which indicates a slower rate of muscle O₂ consumption. Unfavorable changes in skeletal muscle function related to stroke may account for this observation, because Type I and II muscle fibers may be atrophied in SP.⁶ A consequence of the alteration in the Type I muscle fibers is an associated decline in mitochondrial density and oxidative capacity, which may account for the slower V˙O₂ on-kinetics.

Slower V˙O₂ on-kinetics may have been due to a decline in vascular function. Given that endothelial function may be impaired in SP, coupled with findings that V˙O₂ kinetics and blood flow become impaired with peripheral arterial disease,⁷ supports this hypothesis. Further investigation is required to establish the role of blood flow dynamics and mitochondrial function on muscle O₂ consumption in SP to further clarify the mechanisms responsible for our findings.

A limitation of our investigation is that comorbidities such as diabetes, hypertension, and chronic obstructive pulmonary disease may also prolong V˙O₂ kinetics. Additionally, the years (≈7.5) poststroke may account for the slower V˙O₂ kinetics simply because of deconditioning secondary to inactivity. However, we matched SP and healthy control subjects on activity levels and the time poststroke and V˙O₂ kinetics were not related. Future investigations are required to establish the impact of comorbid conditions and stroke type on exercise cardiopulmonary function and V˙O₂ kinetics in SP.

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**Disclosures**
None.

**References**
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