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Augmented exercise pressor response during maximal treadmill exercise is not related to systemic inflammation in stroke survivors

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Abstract

Background: Stroke survivors have exercise intolerance that contributes to reduced quality of life and survival. While exaggerated blood pressure responses during exercise have been documented in other chronic diseases, whether stroke patients have abnormal hemodynamic responses during aerobic exercise remains unexplored.

Objectives: This cross-sectional study aimed to examine whether stroke survivors have exaggerated increases in blood pressure during maximal treadmill exercise and whether these responses may be related to systemic inflammation.

Methods: Forty-six participants (25 stroke survivors, STROKE, and 21 controls, CON) performed a maximal treadmill exercise test via the modified Naughton protocol while blood pressure was measured manually during each treadmill stage. A linear mixed model was used to compare the slope of rise in heart rate and blood pressure within and between groups. Spearmans rho analysis was performed to explore the relationship between these responses and circulating concentrations of inflammatory biomarkers.

Results: The STROKE group exhibited a lower VO2peak (16.4±0.8 vs. 30.0±1.8 ml/kg/min, P<0.001) and a greater rate of increase in systolic blood pressure compared to CON (17.4 ± 1.5 vs. 15.2 ± 1.5 mmHg).
9.9 ± 1.4 mmHg/stage, P<0.001). We observed no relationship; however, between inflammatory biomarkers and the exaggerated hemodynamic responses in the STROKE group.

**Conclusion:** In conclusion, stroke survivors exhibit greater increases in systolic blood pressure during maximal treadmill exercise compared to controls. These responses do not appear to be related to systemic inflammation. Future work should seek to delineate the mechanisms responsible for exaggerated blood pressure responses during exercise in stroke.

**Keywords**

Exercise Pressor Reflex; Neural Control of Circulation; Rehabilitation; Exercise Induced Hypertension

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**Introduction**

Despite extensive resources being allocated to its prevention, stroke remains a leading cause of long-term disability worldwide. Stroke survivors have profound reductions in exercise tolerance and physical capacity that contribute to reduced quality of life and survival. While the mechanisms underlying exercise intolerance in stroke survivors are multifactorial, including muscle atrophy, muscle weakness, pain, autonomic dysfunction, and deconditioning, hemodynamic response during physical activity in this population have not been previously explored. Prior studies in other patient populations characterized by poor physical capacity such as chronic kidney disease and hypertension have demonstrated an augmented increase in blood pressure during exercise that contributes to increased cardiovascular disease (CVD) risk. While blood pressure elevation during physical activity is an adaptive response to meet the increased metabolic demands during exercise, an exaggerated increase in blood pressure during exercise could decrease the efficiency of exercise and increase the risk of adverse cardiovascular events during physical activity. Furthermore, exercise-induced hypertension is associated with an elevated risk of future adverse cardiovascular events, including stroke.

To the best of our knowledge, a careful assessment of hemodynamic responses during exercise in stroke has never previously been explored. Previous studies have demonstrated that inflammation contributes to exaggerated blood pressure responses during exercise in healthy individuals, but this has not been explored in stroke. Since STROKE is associated with a pro-inflammatory state, this may be one mechanism through which exercise blood pressure responses are augmented. Understanding the relationship between systemic inflammation and exercise hemodynamics may inform mechanistic insight into blood pressure regulation during exercise in stroke survivors.

We aimed to contrast the hemodynamic responses during a maximal treadmill exercise test in stroke survivors to that of healthy controls. Additionally, we sought to explore the relationship between systemic inflammation and blood pressure responses during exercise in stroke survivors as an additional aim. We hypothesized that stroke survivors would have exaggerated increases in blood pressure during whole body maximal exercise testing compared to controls, and that elevated serum concentrations of inflammatory biomarkers
would be predictive of exaggerated blood pressure responses during an acute maximal exercise bout following stroke.

Methods

This is a cross-sectional study comprised of data collected at two separate research sites (the Atlanta VA Health Care System, Decatur, Georgia and the VA Maryland Health Care System, Baltimore, MD).

Participants

All data contained within this manuscript conform to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Written informed consent was obtained for community-dwelling stroke participants (STROKE) with residual hemiparetic gait abnormalities (>45 years old, >6 months latency) and preserved capacity for ambulation (either with or without an assistive device). Stroke participants were recruited from VA neurology and primary care clinics and local media advertisements between April 2015 and January 2018. Adequate language and neurocognitive function was evaluated by a study neurologist during a medical screening with a comprehensive history and physical examination to ensure that participants could safely participate in informed consent and maximal exercise testing and to determine eligibility for participation. Further, the Stroke Impact Scale was conducted to evaluate disability and health-related quality of life after stroke (0 to 100, with higher scores indicating better self-reported health). Control participants (CON) had no history of stroke, and had no functional limitations that would prohibit their ability to complete a maximal exercise test (>45 years old). Exclusion criteria for both groups included heart failure, unstable angina, peripheral vascular disease, orthopedic conditions, and other medical or neuropsychiatric conditions (e.g. significant dementia and depression) limiting participation in the exercise intervention.

Maximal Exercise Testing

All participants reported to the laboratory after abstaining from exercise for at least 24 h prior to the testing. Participants on medications took their prescribed medications as scheduled. Participants were instrumented with a 12-lead ECG for assessment of continuous heart rate (HR) during exercise. The exercise test commenced in accordance with the modified Naughton protocol. Briefly, this protocol consisted of 2-min stages with treadmill speed and grade increasing progressively with each stage. Testing was terminated when subjects reached volitional fatigue as communicated verbally. Expired gases were collected and analyzed via a metabolic cart (Cosmed Quark CPET, Concord, CA, USA) and peak oxygen uptake (VO2peak) was determined. HR was recorded via continuous ECG. Blood pressure was measured by a trained investigator during the last 30 seconds of each stage.

Inflammatory Biomarkers

Blood sampling was performed by a trained phlebotomist for measurements of inflammatory biomarkers on a separate study visit. Samples were collected into an EDTA tube after participants had fasted for 12 hours. The sample was immediately centrifuged at 1500RPM.
and plasma was separated and frozen at −80 degrees until analysis. Samples were analyzed in duplicate on a Beckman AU480 chemistry analyzer (Brea, CA) using reagents from Sekisui Diagnostics (CRP), Mercodia (non-esterified fatty acids (NEFA) and oxidized low density lipoprotein (oxLDL), interleukin-6 (IL-6), and vascular cell adhesion molecule-1 (VCAM-1), and Cell BioLabs (nitrotyrosine).

Statistical Analysis

Demographic data between groups were compared via unpaired, two-tailed, T-tests for continuous variables or chi-square analysis for categorical variables. VO\textsubscript{2}\text{peak} and exercise duration were also compared via unpaired, two-tailed, T-tests. A linear mixed model was used to examine the rate of change (i.e. slope) in HR, systolic blood pressure (SBP), and diastolic blood pressure (DBP) over each stage of the treadmill test, and between groups (factor 1: group, factor 2: treadmill stage). Differences in group demographic characteristics (i.e. age and race), as well as medication use (number of meds) were used as covariates in the analyses. The correlation between individual slopes for HR, SBP, and DBP, and circulating concentrations of inflammatory biomarkers were tested via Spearman’s rho (r\textsubscript{s}) analysis. All data are presented as mean ± SE unless otherwise stated. Exact P-values are reported.

Results

Baseline Characteristics

25 STROKE and 21 CON participants were enrolled for participation and all of these participants completed all phases of this study. Demographic data, medication use, and baseline characteristics for study participants are presented in Table 1. Mean stroke latency was 4 ± 1 years. STROKE participants were older than CON and there was a greater proportion of white participants in the STROKE group compared to CON. Overall Stroke Impact Scale score was 61.3 ± 2.6 (range 45–88) indicating mild to moderate disability across the stroke survivors. There were no differences in sex distribution, body mass index, resting blood pressure, or proportion with comorbid hypertension between groups. A greater proportion of the STROKE group was being treated with beta-blockers and statins, due to their history of cerebrovascular disease.

Peak Oxygen Uptake and Exercise Tolerance

The STROKE group exhibited lower peak oxygen consumption compared to the CON group (16.4±0.8, 95% CI [14.8, 17.9] vs. 30.0±1.8, 95% CI [26.5, 33.6] ml/kg/min, P<0.001 Figure 1A.), Cohen’s d=2.39, suggesting a large effect. Additionally, they reached fatigue at an earlier time point than the CON group (365±33, 95% CI [299.7, 430.3] vs. 11,116 ±101, 95% CI [918.5, 1314.7] seconds, P<0.001, Figure 1B). Cohen’s d=2.36, suggesting a large effect.

Hemodynamic Responses during Exercise

Since CON participants were able to exercise longer than STROKE participants, they completed additional stages of the treadmill test (Figure 2, A–C). HR increased during exercise in both groups (P<0.001) with no differences between groups (STROKE=17±1 vs
CON=15±1 bpm/stage, $P=0.07$, Figure 2A). SBP increased during exercise in both groups (Figure 2B, $P<0.001$), and the STROKE group exhibited a greater rate of increase compared to CON (17.4±1.5 vs 9.9±1.4 mmHg/stage, $P<0.001$). DBP did not change during exercise in either group (STROKE=1±0.4 mmHg/stage, CON=0.5±0.7 mmHg/stage, Figure 2C $P\geq0.05$).

**Inflammatory Biomarkers**

After controlling for age and race, we did not observe a significant linear relationship between any inflammatory biomarker and blood pressure responses in the STROKE group (Table 2). Interestingly, we observed a negative correlation between CRP and HR responses ($R=-0.53$, $P=0.0079$, Table 2).

**Discussion**

In this investigation, we report that stroke survivors have decreased exercise capacity, fatigue earlier and exhibit a greater rise in SBP during exercise compared to individuals without a history of stroke. Furthermore, we demonstrate that this augmented hemodynamic response is not related to circulating inflammatory biomarkers in stroke. These findings are clinically relevant as exaggerated blood pressure responses during exercise predict future risk of adverse cardiovascular events\(^\text{10,12}\) and this population is already at higher risk for such occurrences.

Our observation that the STROKE group terminated their exercise test earlier than CON is consistent with previous work demonstrating exercise intolerance in stroke survivors\(^\text{4}\) and reports from qualitative studies suggesting that physical impairments and lack of energy are key limiting factors prohibiting engagement in exercise programs following stroke.\(^\text{19}\) Our primary novel finding of this investigation is that stroke survivors exhibit a greater increase in blood pressure during exercise compared to individuals without a history of stroke. This finding is especially remarkable given that approximately half of the STROKE group was treated with beta-blockers which would be expected to attenuate BP responses. Exercise-induced hypertension is associated with an elevated future risk of adverse cardiovascular events,\(^\text{10,12}\) and is especially pertinent for stroke survivors as this response is also associated with an increased risk of future stroke.\(^\text{13}\)

Exercise is an essential component of stroke rehabilitation,\(^\text{5}\) yet exercise hemodynamics in stroke have not been previously explored. Knowledge regarding these responses is thus needed in order to optimize the safety and efficacy of exercise training in this patient population. One challenge for stroke rehabilitation is to balance the benefits of exercise training with the cardiovascular risk associated with augmented blood pressure responses. Understanding the mechanisms that contribute to exaggerated blood pressure responses during exercise is critical to facilitate the optimization of exercise recommendations for stroke rehabilitation. One factor that has previously been shown to predict exaggerated blood pressure responses in healthy individuals is systemic inflammation.\(^\text{14,15}\) We did not observe a relationship between circulating inflammatory biomarkers and exaggerated hemodynamic responses during exercise in stroke survivors. This finding suggests that other mechanisms may contribute to augmented blood pressure responses during exercise in this population.
Understanding the mechanisms driving the exaggerated blood pressure response during exercise may aid in the pursuit of treatments aimed at ameliorating this undesirable response. Although unexplored in the present investigation, potential mechanisms that may be mediating this response include oxidative stress, endothelial dysfunction, and heightened reflex activation of the sympathetic nervous system, among others. Interestingly, we did observe a moderate negative correlation between plasma CRP concentrations and HR response. Although unexplored, one possibility is that individuals with high CRP concentrations have some degree of cardiomyopathy and thus cannot increase HR to the same extent although this remains to be explicitly tested. Future work should seek to elucidate the precise mechanisms underlying the hypertensive response to exercise post-stroke, so that targeted therapies can be developed to improve exercise hemodynamics in this high-risk patient population.

There are several limitations to our approach that should be mentioned as they relate to interpretation of our findings. First, we included a relatively small sample size and due to the exercise intolerance exhibited in the stroke group, the number of subjects who were able to tolerate the later stages of the exercise was even further reduced. The STROKE group was also significantly older than the CON group and age-related reductions in physical functioning may independently influence the ability to walk on a treadmill. We have included age as a covariate in all analyses to mitigate the potential confounding of this limitation. Second, we did not explore the underlying mechanisms that are responsible for the augmented blood pressure response observed in the STROKE group. It remains unclear whether exercise-induced hypertension in stroke was due to increased sympathetic nervous system activation or increased sensitivity of the alpha-1 adrenergic receptors at the level of the vasculature. Third, the STROKE group, by design, was treated with medications known to influence cardiovascular responses to exercise. We have mitigated the potential confounds of this limitation by controlling for medication use as a co-variate in our analysis. Additionally, the STROKE group still exhibited a heightened SBP response to exercise despite being treated with more antihypertensive medications, suggesting that holding medications prior to testing may have resulted in further augmentation in exercise-induced hypertension in stroke patients. Lastly, inflammatory biomarkers were only measured in the STROKE group. However, the main goal of the analysis was to address whether inflammation is related to augmented blood pressure responses during exercise within stroke patients.

**Conclusion**

In summary, we demonstrate that stroke survivors exhibit an exaggerated blood pressure response during exercise compared to individuals who have not suffered a stroke. Furthermore, this augmented blood pressure response is not related to markers of systemic inflammation. These findings provide insights into hemodynamic responses during exercise in stroke survivors and provide the impetus for future work that should seek to delineate the underlying mechanisms contributing to the exercise-induced hypertension.
Acknowledgements:

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References


Figure 1:
Peak Oxygen Uptake (VO$_2$peak) and Exercise Duration. The STROKE group exhibited lower peak oxygen uptake compared to CON (Panel A, 16.4±0.8 vs. 30.0±1.8 ml/kg/min, P<0.001) and this was accompanied by a shorter time to fatigue (Panel B, 365.0±33.3 vs. 1116.6±101.1 s, P<0.001).
Figure 2:
Mean Hemodynamic Responses during Maximal Exercise Test. Heart Rate (HR) increased with exercise in both groups (Panel A, P<0.001) with no differences between groups (STROKE=17.4±1.5 vs CON=15±1bpm/stage, P=0.07). Systolic blood pressure increased with exercise in both groups (Panel B, P<0.001) and the slope of rise was greater in STROKE compared to CON (17.2±1.5 vs 9.9±1.4 mmHg/stage, P<0.001). There were no differences in diastolic blood pressure during the test within or between groups (STROKE=1±0.4 mmHg/stage, CON=0.5±0.7 mmHg/stage, P≥0.05).
## Table 1.

Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CON</th>
<th>STROKE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>21</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>52.8 ± 8.2</td>
<td>67.08 ± 10.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>21/1</td>
<td>21/4</td>
<td>0.457</td>
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<tr>
<td>Race (Black/White)</td>
<td>18/3</td>
<td>11/14</td>
<td>0.016</td>
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<tr>
<td>Body mass index (kg m(^{-2}))</td>
<td>28.99 ± 4.6</td>
<td>31.52 ± 6.31</td>
<td>0.134</td>
</tr>
<tr>
<td>Resting Seated Systolic Blood Pressure (mmHg)</td>
<td>124 ± 3</td>
<td>129 ± 3</td>
<td>0.30</td>
</tr>
<tr>
<td>Resting Seated Diastolic Blood Pressure (mmHg)</td>
<td>75 ± 2</td>
<td>72 ± 2</td>
<td>0.40</td>
</tr>
<tr>
<td>Hypertension, N (%)</td>
<td>16 (66%)</td>
<td>20 (80%)</td>
<td>0.291</td>
</tr>
<tr>
<td>Diuretic, N (%)</td>
<td>9 (43%)</td>
<td>12 (48%)</td>
<td>0.727</td>
</tr>
<tr>
<td>ACEi/ARB, N (%)</td>
<td>5 (24%)</td>
<td>13 (52%)</td>
<td>0.051</td>
</tr>
<tr>
<td>Calcium Channel Blocker, N (%)</td>
<td>6 (29%)</td>
<td>11 (44%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Beta Blocker, N (%)</td>
<td>0 (0%)</td>
<td>14 (56%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alpha Blocker, N (%)</td>
<td>3 (14%)</td>
<td>1 (4%)</td>
<td>0.217</td>
</tr>
<tr>
<td>Statin, N (%)</td>
<td>5 (24%)</td>
<td>19 (76%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall SIS</td>
<td>-</td>
<td>61.3 ± 2.6</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.

Mean values for inflammatory biomarkers examined in the STROKE group and relationship between these and slope of rise of heart rate, systolic blood pressure, and diastolic blood pressure.

<table>
<thead>
<tr>
<th>Inflammatory Biomarker</th>
<th>Mean ± SE</th>
<th>$r_s$ vs HR Slope</th>
<th>P</th>
<th>$r_s$ vs SBP Slope</th>
<th>P</th>
<th>$r_s$ vs DBP Slope</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-Reactive Protein (mg/L)</td>
<td>2.41 ± 0.27</td>
<td>−0.54</td>
<td>0.0079</td>
<td>0.09</td>
<td>0.6567</td>
<td>0.15</td>
<td>0.4673</td>
</tr>
<tr>
<td>Non-esterified fatty acids (mEQ/L)</td>
<td>0.59 ± 0.05</td>
<td>−0.08</td>
<td>0.71</td>
<td>0.01</td>
<td>0.96</td>
<td>−0.25</td>
<td>0.24</td>
</tr>
<tr>
<td>Oxidized LDL (U/dL)</td>
<td>10.83 ± 0.79</td>
<td>−0.29</td>
<td>0.16</td>
<td>−0.13</td>
<td>0.53</td>
<td>−0.23</td>
<td>0.26</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>24.21 ± 3.82</td>
<td>−0.02</td>
<td>0.93</td>
<td>−0.12</td>
<td>0.58</td>
<td>−0.12</td>
<td>0.56</td>
</tr>
<tr>
<td>VCAM-1 (pg/mL)</td>
<td>7468.5 ± 810.8</td>
<td>0.13</td>
<td>0.55</td>
<td>−0.09</td>
<td>0.66</td>
<td>−0.13</td>
<td>0.54</td>
</tr>
<tr>
<td>Nitrotyrosine (nM)</td>
<td>17.86 ± 2.45</td>
<td>−0.12</td>
<td>0.57</td>
<td>−0.21</td>
<td>0.32</td>
<td>−0.08</td>
<td>0.72</td>
</tr>
</tbody>
</table>

LDL: Low Density Lipoprotein. IL-6: Interleukin-6. VCAM-1: Vascular Cell Adhesion Molecule 1.