Impaired Leg Vasodilatory Function After Stroke
Adaptations With Treadmill Exercise Training

Frederick M. Ivey, PhD; Charlene E. Hafer-Macko, MD; Alice S. Ryan, PhD; Richard F. Macko, MD

Background and Purpose—Resting and reactive hyperemic leg blood flows are significantly reduced in the paretic compared with the nonparetic limb after disabling stroke. Our objective was to compare the effects of regular treadmill exercise (TM) with an active control regimen of supervised stretching (CONTROL) on peripheral hemodynamic function.

Methods—This intervention study used a randomized, controlled design, in which participants were randomized with stratification according to age and baseline walking capacity to ensure approximate balance between the 2 groups. Fifty-three chronic, ischemic stroke participants (29 TM and 24 CONTROL) with mild to moderate hemiparetic gait completed bilateral measurements of lower leg resting and reactive hyperemic blood flow using venous occlusion strain gauge plethysmography before and after the 6-month intervention period. Participants also underwent testing to track changes in peak aerobic fitness across time.

Results—Resting and reactive hyperemic blood flows were significantly reduced in the paretic compared with the nonparetic limb at baseline before any intervention (−28% and −34%, respectively, \(P<0.01\)). TM increased both resting and reactive hyperemic blood flow in the paretic limb by 25% compared with decreases in CONTROL (\(P<0.001\), between groups). Similarly, nonparetic leg blood flow was significantly improved with TM compared with controls (\(P<0.001\)). Peak aerobic fitness improved by 18% in TM and decreased by 4% in CONTROL (\(P<0.01\), between groups), and there was a significant relationship between blood flow change and peak fitness change for the group as a whole (\(r=.30, P<0.05\)).

Conclusion—Peripheral hemodynamic function improves with regular aerobic exercise training after disabling stroke. (Stroke. 2010;41:2913-2917.)

Key Words: blood flow ■ exercise ■ hemiparesis ■ stroke

Disabling stroke causes substantial structural and metabolic abnormalities in the tissues of the hemiparetic leg, resulting in unilateral deficits that disproportionately contribute to systemic cardiovascular risk and overall disability. Paretic limb vasomotor disturbances are among the abnormalities observed by our laboratory and others. We previously reported a 35% reduction in reactive hyperemic blood flow in the paretic leg compared with the nonparetic side in a small number of stroke survivors. These findings suggest that stroke-induced hemodynamic change is likely a major contributor to systemic cardiovascular risk, representing a rehabilitation target when addressing the metabolic and functional disturbances so prevalent in this population.

Some evidence supports the use of regular exercise to improve endothelial flow-mediated vasodilatation in healthy elderly and a variety of disease conditions, including diabetes, hypertension, peripheral arterial disease, chronic heart failure, and spinal cord injury. However, little is known about vascular adaptive capacity in stroke survivors. No studies have assessed the use of progressive, task-oriented aerobic training for modifying the known decrements in hyperemic blood flow in the paretic limb of stroke survivors. For this reason, it remains uncertain whether stroke survivors can perform aerobic exercise at levels requisite to induce vasomotor adaptations in the chronic phase of recovery. Nevertheless, preliminary support for the use of exercise to improve blood flow after stroke is provided by Billinger and colleagues. They used short-term (4 weeks, 3 ×/week) single leg extension/flexion activity in a small number of subacute stroke survivors to show that femoral artery basal blood flow could be improved with resistance training. Still, measures of flow-mediated vasodilatation have never been reported in the context of assessing exercise adaptation after stroke. Hence, further studies are now required to more thoroughly assess the use of commonly applied task-oriented exercise models for eliciting structural and functional vascular adaptation.
We designed the current randomized, controlled trial to test the hypothesis that regularly performed treadmill exercise therapy would be more effective for producing peripheral hemodynamic adaptations than an attention-matched control intervention consisting of elements of conventional stroke rehabilitation.

Methods

Subjects
Participants were recruited from the University of Maryland Medical System and the Baltimore Veterans Administration Medical Center referral networks. Patients with chronic hemiparetic stroke (>6 months) who had completed all conventional physical therapy were sought. Potential participants had mild to moderate hemiparetic gait and demonstrated preserved capacity for ambulation with an assistive device. Baseline evaluation included a medical history and examination. Patients with a history of vascular surgery, vascular disorders in the lower extremities, or symptomatic peripheral arterial occlusive disease were excluded. This study was approved by the Institutional Review Board for research involving humans at the University of Maryland, Baltimore, Md. Written informed consent was obtained from each participant.

Blood Flow Testing
All subjects were assessed under standardized conditions after an overnight fast between 9 and 10 AM. Subsequent to their arrival at the medical center, they were led to a room of consistent temperature (23°C to 25°C) and low ambient noise level. They were then instructed to rest in the supine position for 20 minutes at the time testing preparations were undertaken. Calf blood flow in both legs was obtained separately under resting and reactive hyperemic conditions using venous occlusion mercury strain-gauge plethysmography (Model TL-400; DE Hokanson, Inc, Bellevue, Wash). The right leg was always measured first. Before testing each leg, the calf was elevated above the level of the heart using a dedicated foam pad secured around the widest section of the lower leg. The test for ankle cuff inflation to 220 mm Hg. Basal or resting blood flow was measured before, during, and after each exercise session. Baseline evaluation included a medical history and examination. Patients with a history of vascular surgery, vascular disorders in the lower extremities, or symptomatic peripheral arterial occlusive disease were excluded. This study was approved by the Institutional Review Board for research involving humans at the University of Maryland, Baltimore, Md. Written informed consent was obtained from each participant.

Peak aerobic testing was repeated at the postintervention time point. Participants were randomized to TM or CONTROL after baseline testing using a blocked allocation schema and a computer-based, pseudorandom number generator. Age and severity of deficits were considered in the randomization design. Specifically, separate blocked randomizations were performed according to age (<65 versus ≥65 years) and self-selected walking speed (<0.44 m/s versus ≥0.44 m/s) given the potential impact of these factors on rehabilitation outcomes. Because this was an exercise intervention study, participants could not be blinded to treatment assignment or study hypotheses. An additional limitation of this study is that personnel resource constraints prevented blinded rating of trainers and outcomes testers adding another potential source of unwanted bias to the trial. The possibility of a trainer effect was minimized by having the same staff conduct training sessions for both TM and CONTROL.

Exercise Testing
A physician-supervised treadmill tolerance test at no incline was first performed to assess gait safety and to select walking velocity for subsequent peak exercise testing and treadmill training. Participants minimized handrail support, and a gait belt was worn for safety. For the graded treadmill screening test, all participants who achieved adequate exercise intensities without signs of myocardial ischemia or other contraindications for participating in aerobic training were deemed suitable for entry. The 12-lead electrocardiogram printout from each screening treadmill test was reviewed for myocardial ischemia and other cardiac abnormalities by a cardiologist before granting clearance for ongoing study participation. After a rest interval of at least 1 week to avoid the confounding effects of fatigue, treadmill testing with open-circuit spirometry was conducted to measure peak aerobic fitness. This was done using a previously described treadmill testing (TM) protocol for stroke survivors. Peak aerobic testing was repeated at the postintervention time point.

Data Analysis
Resting and reactive hyperemic blood flows were compared between the paretic and nonparetic legs using a dependent t test. Repeated-measures analysis of variance (3 factors, group×leg×time, 2×2×2) was used to predict values of outcome variables across time, assessing for significant 3-way and 2-way interactions related to changes in both resting and reactive hyperemic blood flow. Pearson correlation coefficients were used to assess the strength of relationship between changes in blood flow and peak fitness. Baseline and repeated values are mean±SD with a 2-tailed probability value of 0.05 required for significance.

Results

Subjects
There were 10 lost to follow-up in the TM group (26%) and 17 lost to follow-up in the CONTROL group (41%). Dropout in TM and CONTROL resulted from medical reasons unrelated to study procedures (n=7 per group) or general compliance issues (n=3 and 10, respectively). There were no serious adverse events resulting from either of the intervention protocols. Of the 53 who completed, 29 (18 men, 11 women) were TM and 24 (11 men, 13 women) were CONTROL. At baseline, there were no significant differences between groups for age, height, weight, or body mass index (Table). There were also no baseline differences between groups for peak fitness or timed walking speed, indicating that the groups were evenly matched in terms of functional capacity. Both the TM and CONTROL groups had approximately the same racial mix (55% and 54% black, respectively) and both groups had similar percentages of participants requiring assistive devices for ambulation. Participant physical and functional characteristics are summarized in the Table.
Blood Flow Differences Between Paretic and Nonparetic Legs

Comparison of resting calf blood flow in the paretic and nonparetic legs for the entire sample (n=53) at baseline revealed a significant 28% difference (1.8±0.8 versus 2.5±1.1 mL/100 mL/min, mean±SD, P<0.01). Likewise, postischemic reactive hyperemic blood flow was reduced by 34% (9.2±5.1 versus 13.9±6.9 mL/100 mL/min, P<0.01) in the paretic limb compared with the nonparetic leg (n=53). These findings were in line with our prior work using a much smaller sample size.6

Effects of TM Versus CONTROL on Peak Fitness

Evidence of an aerobic training effect in the TM group compared with CONTROL is provided by a significant time×group interaction for peak aerobic fitness (P<0.01). Participants in the TM group had a mean improvement of 18% (14.1±4.0 to 16.6±5.6 mL/kg/min, mean±SD) across time compared to a 4% decrease in CONTROL (13.5±3.6 to 12.8±3.9 mL/kg/min).

Effects of TM Versus CONTROL on Lower Leg Blood Flow

Resting blood flow in the paretic and nonparetic legs increased with treadmill training by +25% and +23%, respec-

tively (P<0.001, within group; Figure 1). Conversely, those undergoing the control intervention experienced significant decreases in resting leg blood flow (P<0.05, within group; Figure 1). Similarly, large increases in reactive hyperemic blood flow in both the paretic (+25%) and nonparetic (+22%) legs with treadmill training (P<0.001 within group; Figure 2) contrasted with the decrease in paretic leg reactive hyperemic flow observed across the control intervention (P<0.05, within group). The decrease shown in Figure 2 for the nonparetic leg across the control intervention was not statistically significant. Three-factor analysis of variance revealed that the 3-way interaction terms (group×leg×time) did not achieve significance for both resting (F=0.768, P=0.383) and reactive hyperemic leg flow (F=0.638, P=0.426) but that a 2-way interaction (group×time) did achieve significance for both outcomes (F=40.2 and 34.9, respectively, P<0.001). This indicates that the differing pattern of the response between groups (TM versus CONTROL) did not differ significantly by leg (paretic versus nonparetic). Furthermore, time×group interactions (P<0.001) indicate that the TM intervention was more effective for stimulating blood flow improvement compared with CONTROL. Although TM and CONTROL appear in Figure 2 to have different baseline nonparetic hyperemic flow measures (gray triangle versus gray square), this difference was not significant by independent t test.

Blood Flow Change Versus Change in Peak Fitness

When blood flow changes were compared with changes in peak fitness for the group as a whole (n=53), there were small but significant associations for paretic side reactive hyperemic flow change (r=0.28, P=0.04) and nonparetic side resting flow change (r=0.30, P=0.03).

Discussion

This is the first investigation aimed at determining whether stroke-associated vasomotor function abnormalities can be reversed with regular, task-oriented exercise. Our findings definitively show that progressive, task-oriented treadmill exercise therapy produces large reactive hyperemic blood flow improvements in both the paretic and nonparetic legs after stroke. Given the tight coupling between blood flow and the metabolic characteristics of tissues,4,23 we propose that

- Table. Participant Characteristics by Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>TM (n=29)</th>
<th>CONTROL (n=24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>62±8</td>
<td>60±8</td>
<td>0.27</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>82±23</td>
<td>75±16</td>
<td>0.19</td>
</tr>
<tr>
<td>Height, cm</td>
<td>169±11</td>
<td>169±7</td>
<td>0.96</td>
</tr>
<tr>
<td>Body mass index</td>
<td>28.4±6</td>
<td>26.1±5</td>
<td>0.15</td>
</tr>
<tr>
<td>Walking speed, mph</td>
<td>1.3±0.6</td>
<td>1.3±0.5</td>
<td>0.75</td>
</tr>
<tr>
<td>Peak aerobic capacity, mL/kg/min</td>
<td>14.1±4.0</td>
<td>13.5±3.6</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Mean±SD.

Figure 1. Line graph depicting change in resting leg blood flow (y axis) across the intervention period (x axis). For the paretic leg (black lines), there was a significant increase in resting flow for the TM group (triangles, solid line; **P<0.001 within group) and a significant decrease for CONTROL (squares, dashed line; *P<0.05 within group). For the nonparetic leg (gray lines), there was also a significant increase for TM (**P<0.001, within group) as well as a decrease for CONTROL (*P<0.05 within group). A 2-way interaction effect (time×group, †P<0.001) indicated that change in TM was greater than change in CONTROL. SDs are provided in parentheses next to each mean data point.

Figure 2. This follows the exact same pattern as Figure 1 but represents change in reactive hyperemic leg blood flow across time.
continued exercise therapy in the chronic phase of stroke recovery may be essential for altering the metabolic and functional decrements associated with unilateral tissue deterioration on the paretic side. Of course, longer-term mechanistic studies starting in the earlier stages of stroke recovery will be needed to better support and develop this concept. Observations of concomitant decreases in blood flow parameters during our 6-month control intervention point toward the potentially devastating, rapidly developing vascular health consequences of sedentary living in the chronic phase of stroke recovery. Lastly, correlation between change in aerobic fitness and change in limb blood flow provides additional rationale for adding sufficiently intense aerobic exercise to more conventional forms of stroke rehabilitation.

Earlier studies of blood flow and vasomotor regulation in hemiparetic humans conflicted, reporting either no change or elevated blood flow in the affected limbs. However, our group and others have since produced preliminary evidence related to the detrimental effects of hemiparesis on limb blood flow in small numbers of subjects. The current study, with 53 participants (nearly 3 times the number of our previous report), serves as additional support for the idea that stroke-associated hemiparesis produces marked effects on peripheral blood flow dynamics. Notably, our previous and current findings in stroke survivors suggest that reactive hyperemia in the paretic leg may average approximately half of an age-matched healthy person. Additional context is provided by findings that our nonparetic leg reactive hyperemic blood flow measurements are similar to those previously reported for peripheral arterial disease claudicants. Potential mechanisms responsible for the observed unilateral changes in leg blood flow on the hemiparetic side remain an area of speculation but may include altered autonomic function, enhanced sensitivity to endogenous vasoconstrictor agents, and altered histochemistry and morphology of the vascular network. Furthermore, reductions in limb blood flow have previously been associated with higher proportions of Type II muscle fibers, which is consistent with our findings of paretic-side fiber-type shifts and simultaneous atrophy. Finally, we have reported increased paretic leg skeletal muscle tumor necrosis factor-α, which is known to impair endothelial vasodilatory function.

Stroke-related impairments in flow-mediated vascular function are clinically relevant, because peripheral dysfunction in the endothelium is reflective of systemic disturbances in the larger vascular network. One of the most important characteristics of vessels is the ability to produce changes in vasomotor tone as a result of physical and chemical stimuli and to change blood flow and distribution according to local conditions. Disruptions in this capacity have been implicated in the pathogenesis of metabolic syndrome components as well as functional impairment in humans. Vascular event risk is similarly impacted by blunted peripheral endothelial related vasomotor capacity. Hence, developing therapeutic strategies to address impairments in vasomotor function may be especially relevant in the high-risk, disabled stroke population.

The longitudinal findings of the current study are encouraging and consistent with the degree of exercise-induced vascular adaptation observed in prior investigations with nonstroke cohorts. Although methodological differences with respect to blood flow measurement techniques, training interventions, and populations studied make comparisons between the current study and other investigations challenging, some interesting similarities and contrasts emerge from the small number of blood flow-related exercise trials performed to date. For example, the exercise-induced improvement in limb reactive blood flow among participants with hypertension and peripheral arterial disease was 23% and 30% to 35%, respectively. This is not substantially different from the 27% to 30% relative improvements in healthy elderly or the 25% increase in our stroke survivors. Interestingly, Pierce et al exposed heart transplant recipients to treadmill training and calf blood flow measuring procedures that were similar to the current study and observed a nearly identical improvement in reactive hyperemic flow (+22%). Billinger et al were the first to study blood flow adaptations to exercise after stroke, reporting 40% improvements in basal femoral artery hemodynamics by Doppler after 3 weeks of unilateral resistance training. Our study adds to the literature by measuring changes in flow-mediated dilation using a randomized controlled design and a much longer 6-month aerobic exercise intervention protocol. Collectively, studies on exercise-induced blood flow changes support the idea that stroke survivors maintain similar vascular adaptive capacity compared to other healthy and diseased elderly population groups.

Among the limitations of the current study, beyond those already cited, was the failure to account for whether vascular adaptations were simultaneously occurring in nontrained vascular beds. Specifically, future studies involving stroke survivors might incorporate upper extremity blood flow measurements across lower body exercise interventions to assess the extent to which these interventions have a systemic effect on the vascular tree. Nontrained vascular beds have shown less adaptive capacity in some studies reporting increases in calf blood flow with no concomitant change in forearm blood flow. Conversely, Higashi et al reported a 23% increase in peak vasodilation of resistance arteries of the forearm after a 12-week lower body exercise training program. This was in agreement with other studies showing a systemic effect. Also, it would be useful to study the time course of adaption to training and detraining in chronic stroke given evidence that these changes may occur more rapidly than previously believed. A final limitation relates to the high number of dropouts and the absence of an intention-to-treat analysis. Although the proportion of noncompleters may have been fairly standard for exercise intervention studies of this nature, it is difficult to argue that dropouts did not influence our results to some degree.

In summary, this study provides the first evidence in support of aerobic exercise rehabilitation for addressing hemodynamic disturbances after stroke. We report highly significant changes to resting and hyperemic blood flow in both the paretic and nonparetic legs after exposure to a progressive treadmill training regimen compared with participants exposed to elements of conventional stroke rehabilitation. Our cross-sectional and longitudinal comparisons in the current trial compare favorably with prior investigations,
suggesting vascular adaptations secondary to changes in vessel function and vascular remodeling. Future studies should consider assessments related to the nontrained vasculature as well as the time course of adaptation.

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We thank all of our loyal stroke survivors for their commitment to regular testing and exercise training visits. They are a great inspiration to all who are privileged to interact with them. Additionally, this study would not have been possible without the hard work of the Baltimore Veterans Affairs Exercise Physiology Staff. Their dedication to ensuring participant safety, treatment fidelity, and general satisfaction is essential to the success of our exercise intervention trials.

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Disclosures
None.

References
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脳卒中後の下肢血管拡張機能障害
—トレッドミル運動訓練による適応—

Impaired Leg Vasodilatory Function After Stroke — Adaptations With Treadmill Exercise Training

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脳卒中において麻痺した下肢は麻痺のない下肢に比べて、安静時および反応性充血時の下肢血流量が有意に減少している。本研究の目的は、末梢循環の血行力学的機能に対する定期的なトレッドミル運動（TM）の効果を、指導下のストレッチングによる積極的治療法（対照）と比較することであった。

方法：本研究は無作為対照試験である。各群に被験者をほぼ均等に割り付けるために、年齢およびベースラインの歩行能力によって層別化した。軽度〜中等度の片麻痺歩行のある慢性脳卒中患者53例（TM群29例、対照群24例）に対し、静脈閉塞ストレッキング脈流記録法を用いて、6カ月間の介入前後に下肢の安静時および反応性充血時血流量を測定した。さらに検査により最大有酸素活動能力の経時的変化を追跡した。

結果：介入前ベースライン時に測定では、麻痺群の安静時および反応性充血時血流量は非麻痺群に比べて有意に少なかった（安静時：−28%、反応性充血時：−34%, p < 0.01）。

介入後、TM群では麻痺群の安静時および反応性充血時血流量が25%増加したのに対し、対照群では減少していた（p < 0.001, 群間比較）。同様にTM群では、非麻痺群の血流量も対照群に比べて有意に改善した（p < 0.001）。

TM群では最大有酸素運動能力が18%改善したのに対し、対照群では4%低下した（p < 0.01, 群間比較）。被験者全体でみると、血流量の変化と最大有酸素運動能力の変化の間には有意な関係が認められた（r = 0.30, p < 0.05）。

結論：脳卒中による障害が残った場合には、定期的な有酸素運動訓練を行うことで末梢循環の血行力学的機能が改善する。

Stroke 2010; 41: 2913-2917

図 1
介入前後で示した静脈閉塞血流量（y 軸）の変化を示した棒グラフ。TM群（▲）では麻痺群（黒色の棒グラフ）の安静時血流量が有意に増加したのに対し（**p < 0.001, 群内比較）、対照群（■, 点線）では有意に減少した（*p < 0.05, 群内比較）。同様に、TM群では非麻痺群（灰色の棒グラフ）の血流量も有意に増加したのに対し（**p < 0.001, 群内比較）、対照群では有意に減少した（*p < 0.05, 群内比較）。2方向交互作用効果（時間×群）による、TM群の方が対照群よりも変化が大きいことが示された。各平均データポイントの枠内の値はSDを示す。

図 2
反応性充血時血流量の経時的変化も、図 1 と全く同じパターンを示している。