Improved Cerebral Vasomotor Reactivity After Exercise Training in Hemiparetic Stroke Survivors

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

Background and Purpose—Animal studies provide strong evidence that aerobic exercise training positively influences cerebral blood flow, but no human studies support the use of exercise for improving cerebral hemodynamics. This randomized study in stroke survivors assessed the effects of treadmill aerobic exercise training (TM) on cerebral blood flow parameters compared to a control intervention of nonaerobic stretching.

Methods—Thirty-eight participants (19 in TM group and 19 in control group) with remote stroke (>6 months) and mild to moderate gait deficits completed middle cerebral artery blood flow velocity measurements by transcranial Doppler ultrasonography before and after a 6-month intervention period. Middle cerebral artery blood flow velocity was assessed bilaterally during normocapnia and hypercapnia (6% CO\textsubscript{2}). Cerebral vasomotor reactivity (cVMR) was calculated as percent change in middle cerebral artery blood flow velocity from normocapnia to hypercapnia (cVMR percent) and as an index correcting percent change for absolute increase in end tidal CO\textsubscript{2} (cVMR index).

Results—The TM group had significantly larger improvements than did controls for both ipsilesional and contralesional cVMR index (\(P\leq 0.05\)) and contralesional cVMR percent (\(P\leq 0.01\)). Statin users in the TM group (\(n=10\)) had higher baseline cVMR and lower training-induced cVMR change, indicating that cVMR change among those not using statins (\(n=9\)) primarily accounted for the between-group effects. There was a 19% increase in VO\textsubscript{2} peak for the TM group compared to a 4% decrease in the control group (\(P<0.01\)), and peak fitness change correlated with cVMR change (\(r=0.55; P<0.05\)).

Conclusions—Our data provide the first evidence to our knowledge of exercise-induced cVMR improvements in stroke survivors, implying a protective mechanism against recurrent stroke and other brain-related disorders. Statin use appears to regulate cVMR and the cVMR training response. (Stroke. 2011;42:1994-2000.)

Key Words: cerebral blood flow ▪ exercise ▪ stroke care ▪ transcranial Doppler

Cerebral hemodynamics play an important role in preventing ischemic brain damage.\textsuperscript{1} Functional assessment of the cerebral vasculature is commonly conducted using transcranial Doppler ultrasonography, facilitating cerebral vasomotor reactivity (cVMR) tests that measure the vasodilatory response of cerebral resistance vessels to elevations in arterial carbon dioxide concentration.\textsuperscript{2} Impaired cVMR has been linked to advancing age,\textsuperscript{3} depression,\textsuperscript{4} cognitive decline,\textsuperscript{5} pathogenesis of white matter lesions,\textsuperscript{6,7} and stroke risk.\textsuperscript{8,9} For these reasons, maintenance of adequate cerebral vasomotor reserve capacity is central to protecting brain health and function in aging and high-risk stroke populations.

Although stroke survivors are at high risk for recurrent stroke\textsuperscript{10} and show impaired cVMR,\textsuperscript{11,12} few investigations yield clues on how best to intervene to improve cerebral hemodynamics in this population. Statins are one promising avenue, causing improved cVMR in studies of healthy adults, populations with cardiovascular disease risk, and in those with lacunar infarcts.\textsuperscript{13-15} However, investigations into nonpharmacological nonsurgical approaches for restoring cVMR after stroke are absent from the literature.

Aerobic exercise training can improve vasodilatory function in the systemic circulation in non-neurological human populations,\textsuperscript{16} and animal studies provide preliminary evidence that the benefits of exercise may extend to the cerebral vasculature.\textsuperscript{17-19} Importantly, rodent\textsuperscript{18,19} and primate\textsuperscript{17} studies demonstrate exercise-induced improvements in cerebral blood flow that reduce infarct size and neurological deficits in animal stroke models.\textsuperscript{18} To our knowledge, no human evidence is available to support the use of exercise for enhancing cerebral vasomotor function, despite one study in heart failure patients that improved fitness and cognitive function but failed to improve cVMR determined during breath-holding.\textsuperscript{20} No studies have assessed the effects of aerobic exercise training on cVMR in clinical stroke populations.
The current study sought to determine whether aerobic exercise training improves cVMR or resting middle cerebral artery (MCA) blood flow velocity (BFV) in either the ipsilesional or contralesional hemisphere of chronically disabled stroke survivors. Participants were randomized to progressive treadmill aerobic exercise training (TM) or a nonaerobic stretching control program using elements of conventional stroke rehabilitation therapy to determine whether progressive exercise training was superior for changing cerebral blood flow parameters.

Subjects and Methods
Participants were recruited from University of Maryland Medical System, the Baltimore VA Maryland Health Care System, and University of Maryland Stroke Center Regional Referral Network. Chronic hemiparetic stroke patients with residual mild to moderate hemiparetic gait were screened for participation. Mild-to-moderate hemiparetic gait was defined as readily observable asymmetry of gait including reduced stance time or reduced stance and increased swing time in the affected limb with preserved capacity for ambulation with an assistive device (eg, walker, cane) and/or standby aid as needed. Patients were required to have completed all conventional physical therapy and still present with residual hemiparetic gait deficits >6 months after the index stroke event. Baseline assessment included a review of medical records pertaining to the stroke evaluation, a comprehensive medical history, medication list review, and physical and neurological examinations. Prospective participants with trans-tominal windows insufficient for insonation of the MCA bilaterally were excluded. Procedures used in this study were approved by the Institutional Review Board for research involving humans at the University of Maryland, Baltimore, in accordance with the Helsinki Declaration. Written informed consent was obtained from each participant.

Cerebral Blood Flow Testing
We assessed mean MCA-BFV bilaterally with transcranial Doppler ultrasonography (EME Pioneer TC 2020; Nicolet Vascular). Participants were tested under controlled conditions during normocapnia and hypercapnia before and after the intervention period. Simultaneous monitoring of end-tidal CO2 partial pressure (mm Hg) during transcranial Doppler ultrasonography enabled calculation of the cVMR index (cVMR percent corrected for absolute increase in end-tidal CO2 partial pressure with cVMR percent equal to BFVhypercapnia - BFVnormocapnia/BFVnormocapnia × 100).

Participants arrived for testing fasted between 9:00 AM and 10:00 AM and were positioned in a standardized upright seated position. Participants were fitted with a tight rubber mask around the mouth and nose with a 2-way valve to allow inhalation of either normal air or a gas mixture containing 6% CO2 with monitoring of end-tidal CO2 partial pressure (Sensor Medic 2900, Sensor Medic, Yorba Linda, CA). After a 10-minute rest period (for mask acclimatization and to settle blood flow dynamics), MCA-BFV was preliminarily assessed by hand-held 2-MHz Doppler, allowing correction for slight positional changes. After satisfactory insonation of the MCA through the right transtemporal window, mean MCA-BFV (cm/s) was recorded every 10 seconds for 2 minutes of room air-breathing (normocapnia). Depth of insonation was recorded for reproduction during follow-up assessment. Measurement of MCA-BFV then continued every 10 seconds for a subsequent 2-minute time block during which participants were transitioned to breathing the 6% CO2 gas mixture (hypercapnia). After an additional 10-minute rest period, the identical process of insonation, measurement, and CO2 breathing/monitoring was repeated for the left MCA.

Exercise Testing
During the preliminary treadmill screening test, all qualifying participants achieved adequate exercise intensities without signs of myocardial ischemia or other contraindications for participating in aerobic training. After a 1-week rest interval to avoid effects of fatigue at baseline, exercise testing with open-circuit spirometry was conducted to measure VO2 peak using a graded treadmill test as previously described. Peak aerobic testing was repeated at the 6-month postintervention time point.

Intervention Protocols
The progressive TM protocol consisted of three 40-minute sessions per week at a target aerobic intensity of 60% to 70% heart rate reserve performed over a 6-month training period. Training started at low intensity (40%-50% heart rate reserve) for 10 to 20 minutes and gradually progressed to target levels. Handrail and harness support as well as heart rate monitoring by 2-lead ECG (Polar Electro) were utilized throughout, and vital signs were recorded before, during, and after each exercise session.

The control protocol provided matched duration exposure to health care personnel, implementing components of conventional physical therapy common to stroke. Participants performed 13 targeted active and passive supervised nonaerobic stretching movements of the upper and lower body on raised padded tables 3 times per week for 30 to 40 minutes over 6 months.

Data Analysis
Bilateral baseline normocapnic and hypercapnic MCA-BFV and cVMR were compared between the ipsilesional and contralesional hemispheres using independent Student t test. Repeated-measures ANOVA was used to predict values of outcome variables across time, assessing for significant group-by-time interactions related to changes in MCA-BFVnormocapnia, MCA-BFVhypercapnia, cVMR percent, and cVMR index. Repeated values are mean ± SD, with a 2-tailed P≤0.05 required for significance. Secondary analysis used repeated-measures ANOVA and paired t tests to evaluate between-

Table 1. Participant Characteristics and Medication Use by Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>TM (N=19)</th>
<th>Control (N=19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>61±8</td>
<td>62±10</td>
<td>0.75</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80±17</td>
<td>80±16</td>
<td>0.88</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168±11</td>
<td>171±7</td>
<td>0.35</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>Peak aerobic capacity (mL/kg/min)</td>
<td>14.6±5.0</td>
<td>13.5±3.7</td>
<td>0.44</td>
</tr>
<tr>
<td>NIH Stroke scale score</td>
<td>7.7±5.2</td>
<td>8.9±4.3</td>
<td>0.45</td>
</tr>
<tr>
<td>Walking speed (mph)</td>
<td>1.2±0.6</td>
<td>1.1±0.6</td>
<td>0.58</td>
</tr>
<tr>
<td>6-min walk distance (ft)</td>
<td>669±385</td>
<td>622±345</td>
<td>0.70</td>
</tr>
<tr>
<td>CESD scale score</td>
<td>8.0±8.3</td>
<td>7.6±7.8</td>
<td>0.87</td>
</tr>
<tr>
<td>Smoking status (current/former/never)</td>
<td>16/3</td>
<td>16/3</td>
<td>1.00</td>
</tr>
<tr>
<td>No. with CESD scale scores suggesting depression</td>
<td>4/19</td>
<td>3/19</td>
<td>1.00</td>
</tr>
</tbody>
</table>
| Continuous variables are mean ± SD compared using independent t test and categorical variables between groups were compared between groups using Fisher exact test.

ACE indicates angiotensin-converting enzyme; CESD, Centers for Epidemiologic Studies Depression; NIH, National Institutes of Health; TM, treadmill aerobic exercise training; TZD, thiazolidinedione.
subgroup and within-subgroup effects for cVMR change in TM participants using and not using statins. Additionally, the Pearson correlation coefficient quantified the strength of the relationship between change in VO₂ peak and change in cVMR.

**Results**

**Subjects**
Of 119 screened and 51 with baseline transcranial Doppler ultrasonography assessments, 38 stroke survivors with residual hemiparetic gait (19 TM and 19 controls) completed follow-up bilateral measurements with simultaneous end-tidal CO₂ partial pressure monitoring after the 6-month intervention period. The completers in each group were reasonably well-matched at baseline, with no significant differences between groups for age, height, weight, or body mass index (Table 1). The groups were exactly matched for percentages of men (58%) and blacks (47%). Table 1 also shows no baseline difference between groups for peak fitness,
timed walking speed, 6-minute walk distance, and National Institutes of Health Stroke scale score, indicating that the groups were fairly evenly matched in terms of functional capacity. Other comparisons made related to depression scores, smoking status, and medication use also showed no differences. Table 2 depicts stroke side, stroke subtype, available imaging, and assistive device utilized by each subject in both groups. Only 12 of 38 subjects had vessel status imaging by MRA, showing no intracranial vessel stenosis in this subgroup. However, review of normocapnic MCA-BFV in the total sample suggests that intracranial stenosis may have been present in 1 treadmill participant and 2 control participants. Also, review of imaging records, medical records, and ultrasound findings showed that hemodynamically significant carotid artery stenosis was present in 1 subject in each group at the time of study.

Baseline Interhemispheric MCA-BFV and cVMR Comparisons

For the entire sample (n=38), baseline comparisons between hemispheres for cerebral blood flow parameters revealed several differences. MCA-BFV during normocapnia was 18% lower on the ipsilesional side (P<0.05) and hypercapnic MCA-BFV was reduced by 19% on the side of the stroke (P<0.01). However, there were no interhemispheric differences observed for either cVMR percent or cVMR index (Table 3).

### Table 3. Baseline Interhemispheric Comparisons of Blood Flow Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Ipsilesional (n=38)</th>
<th>Contralesional (n=38)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA-BFV, normocapnia (cm/s)</td>
<td>39.4±16.1</td>
<td>47.8±15.8</td>
<td>0.026*</td>
</tr>
<tr>
<td>MCA-BFV, hypercapnia (cm/s)</td>
<td>54.1±20.4</td>
<td>67.0±20.6</td>
<td>0.008†</td>
</tr>
<tr>
<td>cVMR %</td>
<td>38.9±14.8</td>
<td>41.9±17.4</td>
<td>0.419</td>
</tr>
<tr>
<td>cVMR index (% per mm Hg)</td>
<td>4.0±1.7</td>
<td>4.3±1.9</td>
<td>0.500</td>
</tr>
</tbody>
</table>

Mean±SD.  
BFV indicates blood flow velocity; cVMR, cerebral vasomotor reactivity; MCA, middle cerebral artery; SD, standard deviation.  
*P<0.05.  
†P<0.01.

### Table 4. Effects of Treadmill and Control Interventions on Cerebral Blood Flow Outcomes

<table>
<thead>
<tr>
<th>Measure</th>
<th>Before TM (n=19)</th>
<th>After TM (n=19)</th>
<th>Before Control (n=19)</th>
<th>After Control (n=19)</th>
<th>P Time× Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA-BFV, normocapnia, I (cm/s)</td>
<td>36.2±10.3</td>
<td>38.1±9.9</td>
<td>42.7±20.1</td>
<td>44.9±18.4</td>
<td>0.836</td>
</tr>
<tr>
<td>MCA-BFV, normocapnia, C (cm/s)</td>
<td>49.7±14.4</td>
<td>47.7±12.5</td>
<td>45.8±17.3</td>
<td>48.1±15.3</td>
<td>0.031*</td>
</tr>
<tr>
<td>MCA-BFV, hypercapnia, I (cm/s)</td>
<td>49.2±14.0</td>
<td>53.6±13.8</td>
<td>59.1±24.7</td>
<td>60.8±22.6</td>
<td>0.281</td>
</tr>
<tr>
<td>MCA-BFV, hypercapnia, C (cm/s)</td>
<td>66.3±16.8</td>
<td>68.1±16.6</td>
<td>67.7±24.2</td>
<td>68.1±23.6</td>
<td>0.667</td>
</tr>
<tr>
<td>cVMR %, I</td>
<td>36.6±14.8</td>
<td>42.0±15.2</td>
<td>41.2±14.8</td>
<td>38.6±17.5</td>
<td>0.118</td>
</tr>
<tr>
<td>cVMR %, C</td>
<td>34.6±12.0</td>
<td>44.3±21.2</td>
<td>49.3±19.1</td>
<td>41.1±13.6</td>
<td>0.007†</td>
</tr>
<tr>
<td>cVMR index, I</td>
<td>4.1±1.9</td>
<td>5.2±2.7</td>
<td>3.9±1.5</td>
<td>3.6±1.7</td>
<td>0.031*</td>
</tr>
<tr>
<td>cVMR index, C</td>
<td>3.9±1.8</td>
<td>5.2±4.9</td>
<td>4.7±2.1</td>
<td>4.2±1.4</td>
<td>0.052*</td>
</tr>
</tbody>
</table>

Mean±SD.  
BFV indicates blood flow velocity; C, contralesional hemisphere; cVMR, cerebral vasomotor reactivity; I, ipsilesional hemisphere; MCA, middle cerebral artery; TM, treadmill aerobic exercise training; SD, standard deviation.  
*P<0.05.  
†P<0.01.

### Training-Induced Changes in Peak Fitness

Evidence of an aerobic training effect for TM is provided by comparing changes in VO2 peak between groups across time. There was a 19% increase in VO2 peak among TM trainers (14.6±4.9 to 17.4±6.99 mL/kg/min, mean±SD) compared to a 4% decrease in controls (13.5±3.7 to 12.8±4.5 mL/kg/min), producing a significant time-by-group interaction (P<0.01). Change in peak fitness was accompanied by a 16% increase in walking speed among TM trainers (1.24±0.61 to 1.44±0.64 mph) compared to no change in controls (1.17±0.57 to 1.18±0.62; P=0.06 between groups). Additional evidence of functional improvement subsequent to progressive treadmill training is provided by 6-minute walk changes across the intervention period. There was a significant time-by-group interaction for TM trainers (669±385 to 796±411 feet) versus controls (622±345 to 647±350) for 6-minute walk distance (P=0.012). There were no significant between-group or within-group training effects for either systolic or diastolic blood pressure.

### Training-Induced Changes in MCA-BFV and cVMR

Between-group comparisons for cerebral blood flow measures are provided in Table 4. As shown, there was a significant time-by-group interaction for cVMR percent in the contralesional hemisphere (P=0.01) and for cVMR index in both hemispheres (P<0.05). On the ipsilesional side, the mean cVMR index increased by 27% in the TM group compared to a small 4% decrease among control participants (P=0.05). Between-group differences for cVMR percent on the ipsilesional side did not reach statistical significance (P=0.118). Mean contralesional cVMR percent increased by 28% in the TM group compared to a 16% decrease for the control group during the 6-month intervention time period (P<0.01). Similarly, cVMR index increased by 33% in the contralesional hemisphere, which was significantly different than the decrease observed in controls (P<0.05). Subsequent within-group analyses for the blood flow measures that had revealed time-by-group differences showed that all within-group TM increases were statistically significant (P≤0.05)
but that none of the control group decreases achieved statistical significance.

Importantly, change in peak fitness across the TM intervention was positively correlated with change in cVMR index ($r=0.55$; $P<0.05$), implicating aerobic capacity change as a partial mediator of adaption in cerebral vasomotor function after stroke. As anticipated, the cVMR values observed in those using statins were much higher at baseline ($+53\%$; $P<0.05$; Figure A, B). Further, we compared the cVMR TM training response in those using and not using these medications. Despite a much larger training response in those not using statins ($n=9$) compared to those using statins ($n=10$), there was not enough statistical power to demonstrate a between-subgroup effect (Figure 1A, B). However, it can be stated that the within-group medication subgroup analyses revealed significant training-induced improvements only in those not using statins ($n=9$) compared to insignificant improvements within the statin subgroup ($n=10$; Figure 1A, B). This implies that our observed between-group training effect was driven primarily by the nonmedicated subgroup within the TM group and that little to no additional training-derived benefit is to be attained by those who have already obtained the statin-induced benefit.

**Discussion**

This is the first randomized study to our knowledge showing improved cerebral vasomotor reactivity with exercise training in humans. Our results demonstrate that aerobic treadmill training improves cVMR but not normocapnic MCA-BFV in individuals with chronic hemiparetic stroke. These improvements in cVMR were associated with a significant $19\%$ increase in VO$_2$ peak; a fitness gain equal in magnitude to that expected for older nondisabled and hemiparetic subjects participating in moderate intensity aerobic training. The clinical implications are that exercise may confer cerebrovascular health benefits after stroke. Although stroke survivors with severe heart disease or unstable angina are inappropriate for progressive treadmill training, the current results do further demonstrate the tolerability and additional benefits related to such an intervention for those with moderate disability and reasonable cardiac function.

Among the remaining questions subsequent to our initial findings is whether exercise therapy can add to the cerebral blood flow benefits that have been previously known to occur from statins. Whereas our preliminary findings in small numbers cast doubt on the possibility of additive benefits, it is important that larger studies be undertaken exploring critical dose–effect questions with respect to the way statins impact on the cVMR training response. Additionally, it would be useful to test whether higher-intensity training protocols produce additive benefits in stroke survivors using statins.

Diminished cVMR is reported in normal aging and in individuals with a variety of vascular-related disease conditions. It exhibits diurnal variations, reaching low points during morning hours when stroke events are most prevalent. Both symptomatic and asymptomatic carotid artery stenosis are well-known contributors to impaired cVMR, with vasomotor response to CO$_2$ lower on the stenotic side and improving after carotid endarterectomy. Previous investigations report that impaired cVMR predicts higher stroke risk, although one recent study suggests basal MCA-BFV is more important to stroke risk than cVMR.

Diminished cerebrovascular reserve can lead to hypoxia in vulnerable areas of the brain, negatively affecting brain health in ways beyond stroke and stroke risk. For example, those presenting with Alzheimer disease and vascular dementia show lower cerebral flow velocities and cVMR compared with controls. Further, decreased cVMR is related to cognitive impairment, and dysfunction of cerebral vascular autoregulation contributes to the pathogenesis of white matter lesions in advancing age. Cerebral white matter lesions are an early marker of cerebrovascular disease and are considered a risk factor for the development of stroke and cognitive impairment. Finally, depressive symptoms, which are highly prevalent after stroke, are linked to reduced blood flow velocities and lower vasomotor reactivity.

Despite the established relevance of cVMR to general brain health and function, only one study has previously tested the effects of exercise training on cVMR. Briefly,
Tanne et al\textsuperscript{20} studied congestive heart failure patients \(n=20\) over the course of 18 weeks of TM and found no changes in cVMR, although training-induced improvements in physical function and cognition were reported. This study differs from the current investigation not only with respect to the population studied and the shorter training duration but also as related to the technique used for deriving cVMR. The previous study\textsuperscript{20} used the “breath-holding index” to represent cVMR, and use of breath-holding to induce a cerebral vasomotor response limits comparison with the current study. Our study in chronic stroke reports lower normopacmic and hypercapnic MCA-BV in the ipsilesional hemisphere but no difference in cVMR between sides. Healthy age-matched individuals without stroke typically have cVMR percent values in the mid 50s,\textsuperscript{5,30} indicating that stroke survivors in this study had mean bilateral cVMR percent impairments that equated to a 30% reduction compared to age-matched healthy individuals without stroke. Our findings that cVMR index increased by 27% and 28% with TM in ipsilesional and contralesional hemispheres, respectively, suggest aerobic exercise may restore a substantial proportion of the vasomotor reactivity that is lost bilaterally after a unilateral hemispheric stroke.

Our study did not determine the durability of exercise treatment effects or their long-term exercise effects on cerebrovascular health. Further, we did not investigate the potential for exercise to improve cVMR in earlier phases of stroke, which may prove more powerful in secondary prevention. Instead, we opted to first investigate the effects of exercise on cerebral hemodynamic measures in a chronic stroke cohort with stable deficits. Larger clinical studies should be considered that define the long-term health benefits of exercise to prevent cerebral ischemic events in stroke survivors across the different phases of recovery and in aging individuals with chronic vascular–metabolic risk factors for stroke. Of equal importance, based on the current findings, is coming to a final understanding about the potential for exercise training to affect cVMR change in stroke survivors using statins. In addition, future studies should consider assessing cognitive function outcomes in conjunction with cerebral blood flow parameters to determine the relationship of one with the other across exercise intervention periods after stroke.

\section*{Conclusions}

In summary, these randomized study results provide the first human evidence to our knowledge that exercise training can improve bilateral cVMR in chronic hemiparetic stroke. Interpretation of our results should take into account the small sample size, incomplete imaging records, and the differential training responses in those using and not using statin medications. Larger studies should be conducted to confirm our current findings and to determine the dose–effect of statin use on cVMR response, the optimal exercise dose intensity for improving cVMR, and the relationship of cVMR improvements to changes in a wide variety of motor function and cognitive outcomes. Another future direction might entail developing a better understanding of how cerebral blood flow measures relate to depression both before and after a training intervention. Finally, it would be useful to establish the durability and long-term effects of exercise on brain structural integrity and function for aging individuals with stroke and stroke risk factors.

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\section*{Disclosures}

None.

\section*{References}


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