Time Course of Flow-Mediated Dilation and Vascular Endothelial Growth Factor following Acute Stroke

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Objectives: People after stroke demonstrate alterations in vascular endothelial function measured by flow-mediated dilation. Limited information is available in the literature on possible protective factors following stroke. The aims of the secondary analysis were (1) to characterize the time course of vascular endothelial function using flow-mediated dilation at 72 hours after stroke and 1 week later during inpatient stroke rehabilitation and (2) to determine whether flow-mediated dilation was related to vascular endothelial growth factor, brain-derived neurotrophic factor, or estimated prestroke peak oxygen uptake. *Methods:* Flow-mediated dilation using Doppler ultrasound was assessed in bilateral brachial arteries at the defined time points. Flow-mediated dilation and blood draws occurred on the same day between 7:30 AM and 9:00 AM following an overnight fast. Enzyme-linked immunosorbent assay was used to quantify plasma vascular endothelial growth factor and brain-derived neurotrophic factor values. A nonexercise estimate was used to calculate prestroke peak oxygen uptake. *Results:* We have shown that between-limb differences are evident within 72 hours after stroke and remain 1 week later during inpatient rehabilitation. Higher values for vascular endothelial growth factor were associated with increased flow-mediated dilation at both time points. Higher estimated prestroke peak oxygen uptake was related to flow-mediated dilation. Brain-derived neurotrophic factor was not related to any outcome measures. *Conclusions:* Unique vascular adaptations start early after stroke in the stroke-affected limb and remain through inpatient stroke rehabilitation. Vascular endothelial growth factor and prestroke physical activity may have a protective role in vascular function following stroke. Future work should focus on mechanistic pathways for preservation of vascular health.

Key Words: Flow-mediated dilation—vascular endothelial function—acute stroke—echocardiography—rehabilitation—ultrasound.

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Introduction

A healthy vascular endothelium is essential for regulating the function of the blood vessel and delivery of blood to tissues. Negative physiological adaptations can occur as a result of chronic disease[1-3] including stroke.[3-7] Our previous work found that vascular endothelial function using flow-mediated dilation (FMD) was reduced in the stroke-affected arm.[4] Unilateral adaptations are not typically observed in healthy young and older adults[8,9] and can have the potential to affect blood flow delivery during exercise or activities of daily living.[6]

Reduced blood flow and arterial diameter could not only have implications for physical activity in the community but may also influence rehabilitation where optimal blood flow regulation is needed for exercise, standing activities, and walking. Therefore, we have been interested in better understanding the timeline of when these unilateral vascular adaptations begin after stroke and the relationship of any protective factors that may be a target for future interventions. We have previously shown that people with acute stroke have reduced FMD when compared to age- and gender-matched controls.[5] A recent publication reported similar findings within the first 10 days of stroke.[3] The authors reported patients with stroke had reduced FMD even when compared to patients with similar cardiovascular risk factors. This finding highlights that there may be factors uniquely related to stroke.

The purpose of this secondary analysis was to first characterize the time course of vascular endothelial function using FMD early after stroke and then 1 week later during inpatient rehabilitation. Second, we examined whether vascular endothelial growth factor (VEGF) and prestroke estimated peak oxygen uptake (peak VO_2) was related to FMD. We have previously reported that within 72 hours after stroke between-limb differences exist for vascular endothelial function.[5] Therefore, we hypothesized we would detect between-limb differences in FMD at 1 week after stroke. We wanted to explore whether VEGF and prestroke estimated peak VO_2 were related to FMD measures. We hypothesized that (1) VEGF and (2) prestroke estimated peak VO_2 would be moderately related to FMD. We also measured brain-derived neurotrophic factor (BDNF) from our blood samples to explore relationships to our selected outcome measures.

Materials and Methods

Participants

Participants admitted to University of Kansas Hospital between March 2013 and April 2015 with acute stroke were approached for enrollment into the study. Because this is a secondary analysis, these study participants have been described elsewhere.[5] Briefly, patients were admitted to the acute stroke unit and screened for the following inclusion criteria: (1) diagnosis of unilateral stroke from neuroimaging, (2) ability to provide consent within 72 hours of admission to the stroke unit, and (3) age between 30 and 80 years. Individuals were not enrolled if the following exclusion criteria were present: (1) acute renal failure, (2) ischemic cardiovascular event or coronary artery bypass surgery less than 3 months before stroke, (3) severe peripheral artery disease, (4) diagnosis of congestive heart failure, and (5) inability to maintain position of the upper extremity to provide access to the brachial artery during ultrasound scanning.

The study was approved by the Human Subjects Committee at the University of Kansas Medical Center, which complies with the Declaration of Helsinki [approval number 12490]. Institutionally approved written consent was obtained before enrollment from all participants or the surrogate decision maker.

Questionnaires and Medical Information

We have previously published data on the use of a nonexercise estimate for prestroke peak VO_2 in acute stroke.[10,11] The medical record was used to gather information on heart function using ejection fraction (%) from the ultrasound report because low cardiac output could affect vascular endothelial function.

Flow-Mediated Dilation

FMD Time 1 was performed within 72 hours of admission to the acute stroke unit,[5] and Time 2 was performed within the inpatient rehabilitation setting 1 week later. FMD was conducted using Doppler ultrasound on bilateral brachial arteries in the upper extremities using previously published methodology.[4,5] Participants refrained from food or caffeine for 12 hours before the ultrasound scan, and no medications were given from midnight until after the procedure. Vasoactive medications were withheld overnight.[5,12] All ultrasound scans occurred within a 2-hour window in the morning between 7:30 AM and 9:00 AM.

We have previously reported on our FMD methodology[4,5] and follow published recommendations for conducting FMD[13] using Doppler ultrasound. All images were stored on a computer and analyzed off-line using specialized software (Brachial Analyzer, Medical Imaging Applications, Coralville, IA).

Blood Analysis

Approximately 10 mL of venous blood was obtained from each participant on the same day as the Time 1 FMD procedure. Blood was immediately stored on ice to be transported to the laboratory for processing and storage at –80°C within 1 hour of collection from the participant.[5] After all samples were collected from participants, the University of Kansas Biobehavioral Measurement Core (P30 HD002528) performed the assays to quantify VEGF and BDNF.