Journal of the American Society of Hypertension ■(■) (2018) 1–9

Research Article

Arginine impairs endothelial and executive function in older subjects with cardiovascular risk

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Manuscript received January 19, 2018 and accepted July 3, 2018

Abstract

Neurovascular coupling, the relationship between cerebral blood flow and neuronal activity, is attenuated in patients with impaired executive function. We tested the hypothesis that peripheral vascular function may associate with executive function in older subjects with cardiovascular risk factors and that treatment with the antioxidant L-arginine would improve both vascular and executive function. Nineteen subjects with type 2 diabetes mellitus and/or controlled hypertension were enrolled. Subjects were treated with L-arginine or placebo for 4 days in a randomized, double-blinded, cross-over study. Brachial artery vascular function, peripheral artery tonometry, and Trail Making Test Part B testing were performed on day 1 and day 4 during each condition. L-arginine significantly reduced the digital reactive hyperemia index, and the comparison of changes against placebo was significant ($P = .01$). With executive function testing, we observed a significant interaction between treatment and order. Restricting the analysis to the first treatment period, subjects treated with placebo decreased their Trail Making Test Part B times by 57.3 ± 52.5 seconds from day 1 to day 4 ($P = .01$) while those treated with arginine had no significant change (6.4 ± 18.4 seconds worse, $P = .37$). In addition, L-arginine was associated with increased mean arterial pressure from 88 ± 9 mm Hg to 92 ± 11 mm Hg, which trended toward significance. L-arginine treatment worsened digital microvascular and executive function in older subjects with cardiovascular risk factors. These data further support a link between vascular and executive function. J Am Soc Hypertens 2018;■(■):1–9. © 2018 American Heart Association. All rights reserved.

Keywords: Aging; cognitive impairment; endothelial function; nitric oxide.

Introduction

We have previously reported on the close relationship between cerebral blood flow and neuronal activity in response to cognitive work, termed neurovascular coupling (NVC).[1] NVC was intact in healthy patients and attenuated in patients with impaired executive function, suggesting a relationship between vascular and executive function.[2] This linkage between vascular function and health has been noted in a large number of domains. For example, a reduction in conduit artery nitric oxide bioavailability (endothelial dysfunction) has been associated with worse cardiovascular health, such that abnormal endothelial function associates with the presence of coronary artery disease, the risk of myocardial infarction, and death.[3] Patients with executive function decline are commonly older with risk factors for atherosclerosis.[4,5] Diminished middle cerebral artery blood flow velocity in response to cognitive stress, coupled to a risk factor state, suggests that an attenuation in endothelium-derived nitric oxide bioavailability may represent a common pathophysiology underlying vascular and executive function.

In a cohort of older subjects with cardiovascular risk factors, we tested the hypothesis that two measures of systemic vascular function, brachial (conduit) artery flow-mediated vasodilation (FMD) and digital pulse amplitude tonometry, would improve with the endothelial nitric oxide synthase

Clinical Trial Registration: www.clinicaltrials.gov (NCT01482247).

Conflict of interest: None.

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https://doi.org/10.1016/j.jash.2018.07.002

(eNOS) co-factor L-arginine. Furthermore, we tested whether vascular function in these separate vascular beds associates with neurocognitive function and whether treatment with L-arginine would improve executive function in association with improved endothelial function.

Methods

Nineteen subjects aged 70 years and older with diabetes mellitus type 2 and/or controlled stage 1 hypertension by guidelines from the The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (systolic blood pressure [SBP] <160 and diastolic blood pressure [DBP] <100 mm Hg) were enrolled. Hypertension was defined by blood pressure ≥140/90 mm Hg on two separate visits or by preexisting diagnosis of hypertension and subject taking antihypertensive medication. Type 2 diabetes mellitus was defined by glycated hemoglobin (HbA1c) ≥ 6.5% or by preexisting diagnosis of diabetes and subject taking oral hypoglycemia agents. Screening blood pressure was taken as the median of three consecutive recordings performed manually with a sphygmomanometer, with participants seated. Participants were recruited from the local Boston community through institutional review board–approved advertisements placed online and in print media. To obtain the 19 subjects who completed the protocol, after consent was obtained, a screening transcranial ultrasound was performed; 13 people whose cerebral arteries could not be insonated were excluded. Other exclusion criteria included intact executive function, as measured by a Trail Making Test Part B (TMTB) test above the 25th percentile based on normative reference data[1,6] (19 people excluded for intact function), history of stroke, myocardial infarction, or diagnosis of dementia. Studies were performed in accordance with Declaration of Helsinki, approved by the institutional review committee, and all subjects signed informed consent before participation.

Once enrolled, subjects were randomized to receive one of two sequences of oral L-arginine and placebo in this double-blinded crossover study (Figure 1). Arginine was chosen for this study because of its rapid effect on eNOS.[7,8] Outpatient visits were performed at the Clinical Trials Center and Vascular Research Laboratory at the Brigham and Women's Hospital. During the study period, subjects continued to take their usual daily medications, including those for diabetes and for hypertension. This study was registered on clinicaltrials.gov (NCT01482247).

Study Visits

Peripheral and cerebral vascular function was measured on four outpatient visits, before and after separate 3-day trials of oral L-arginine and placebo (Figure 1). Vascular studies included peripheral arterial tonometry (PAT) using plethysmography, and brachial artery FMD. After the first baseline study, subjects were given an equal number of identically appearing placebo or L-arginine packets dosed 7 g each (BioKyowa Inc., Cape Girardeau, MO.). Subjects began the study drug after their first baseline study and consumed two doses of study supplement on day 1 (14 g), three doses on days 2 and 3 (21 g), and two doses on day 4 (21 g). On day 4, subjects took the final dose of study medication in the hospital and then again had PAT and FMD responses measured. There was a 4-week washout, followed by two final study days, before and after

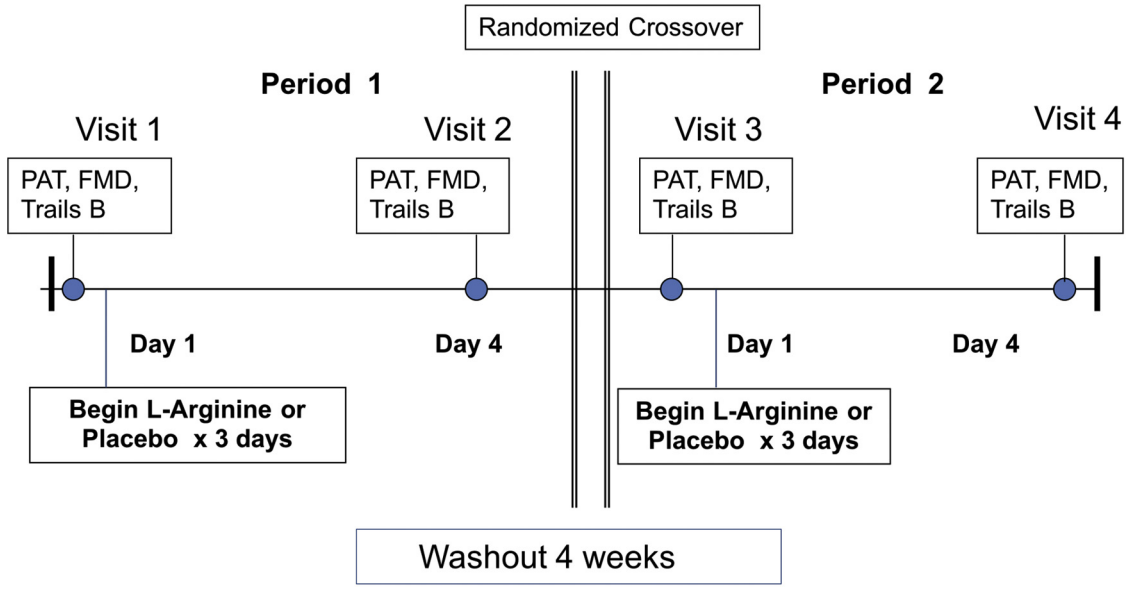

Figure 1. Study schema. FMD, flow-mediated vasodilation; PAT, peripheral arterial tonometry; Trials B, Trail Making Test B.

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