Demographic and Systemic Hemodynamic Influences in Mechanisms of Cerebrovascular Regulation in Healthy Adults

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Objectives: A competent cerebrovascular regulation maintains an adequate cerebral blood flow by 3 major mechanisms: cerebral autoregulation (CA), vasomotor reactivity (VMR), namely to CO_2, and neurovascular coupling (NVC). However, most studies generalize their results based on a response to a single parameter. Using a full battery of neurovascular stress tests, our study aims to evaluate the relationships among grades of CA, VMR, and NVC, and how their interplay is influenced by demographic and systemic hemodynamic factors. *Methods:* Fifty-eight healthy adults were recruited to fit each decade age stratum from 20 to 80 years old with similar sex ratio. Arterial blood pressure (Finometer), cerebral blood flow velocity in the middle cerebral arteries (transcranial Doppler), electrocardiogram, and end-tidal CO_2 were monitored. We assessed CA by transfer function analysis, VMR at hypocapnia and hypercapnia (carbogen 5%), and NVC response during the N-Back Task. The Montreal Cognitive Assessment scores were recorded. *Results:* Neurovascular stress tests were not affected by age or gender, and no correlation was found between their outputs ($P > .05$). Systemic hemodynamic parameters during tasks as well as cognitive scores had no correlation with cerebrovascular measurements ($P > .05$). *Conclusions:* Age and gender do not have major influence on the 3 major cerebrovascular regulation mechanisms. Our results also pinpoint the fact that neurovascular stress tests measure different aspects of cerebrovascular control, and that their outputs are uncorrelated and cannot be used interchangeability. Being independent of age and cognitive status, neurovascular stress tests seem adequate for studying several cerebrovascular conditions affecting the aging brain. **Key Words:** Cerebrovascular reactivity—cerebral blood flow—cerebral autoregulation—vasomotor reactivity—neurovascular coupling—transcranial Doppler.

Introduction

Harmonious control of the cerebrovascular bed is crucial for maintaining an adequate cerebral blood perfusion in response to a myriad of vasoactive stimuli.[1] In order to compensate the high metabolic rate and limited energy stores of brain tissue, a complex interplay among metabolic,[2] neuronal,[3-5] and pressure- and shear-dependent[2,3,6] myogenic mechanisms modulates cerebral resistance, allowing the cerebral vasculature to constrict or dilate in response to hemodynamic and neurophysiological stimuli.[1]

Transcranial Doppler is a powerful and versatile tool for noninvasive assessment of intracranial vessels. It allows easy access to the health of the cerebral microvascular bed using neurovascular tests.[2,7,8] These procedures allow the evaluation of 3 major physiological processes

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Received July 29, 2016; revision received August 24, 2016; accepted December 5, 2016.
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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.12.003

that underlie cerebral blood flow preservation: (1) cerebral autoregulation (CA), which is the capacity of the cerebral blood vessels to maintain constant cerebral blood flow regardless of the fluctuation in arterial blood pressure (ABP)[7]; (2) vasomotor reactivity (VMR), the response blood vasoactive substances like carbon dioxide (CO_2)[2]; and (3) neurovascular coupling (NVC), or functional hyperemia, which adapts local flow in response to neuronal activity.[1,2,9,10]

Impairment of cerebrovascular regulation has been linked to several disorders, such as Alzheimer[11,12] and Parkinson[13] diseases, trauma,[14] subarachnoid hemorrhage,[15] carotid artery disease,[16] stroke,[17] metabolic diseases,[18] and autonomic failure.[3,19] However, in most reports, considerations about global cerebrovascular regulation status are supported by only one of these components. Therefore, there is a lack of evidence on the interplay among CA, VMR, and NVC in both healthy and pathologic states, and how age, gender, and other demographic factors influence them per se, regardless of disease.

Using a comprehensive neurovascular stress tests battery, this study seeks to determine how different mechanisms of cerebrovascular control (CA, VMR, and NVC) relate to each other in healthy adults and how they might be influenced by age, gender, and systemic hemodynamic factors.

Materials and Methods

This study was conducted in São João Hospital Center, a university hospital in Porto, Portugal. It was approved by the appropriate local institutional ethical committee and performed in accordance with the Declaration of Helsinki ethical standards. All participants gave written and signed informed consent.

Population Studied

Subjects were selected by advertising within university facilities. We predefined to include 10 Caucasian participants, with a sex ratio of 1:1 in each decade of age strata, ranging from 20 to 80 years old. All participants fulfilled a comprehensive questionnaire to exclude common vascular risk factors (hypertension, diabetes, and smoking), history of vascular disease (e.g., heart failure, atrial fibrillation, etc.), or any neuropsychiatric disease affecting central or autonomic nervous system. Systolic and diastolic blood pressures were averaged from 3 measurements in the sitting position with an oscillometric cuff (Omron M6, Kyoto, Japan). Body mass index was calculated. Participants above 35 years old underwent cervical and transcranial ultrasound examinations (Vivid e, GE, Little Chalfont, UK) to exclude hemodynamically significant carotid stenosis. The Montreal Cognitive Assessment (MoCA) test, which is sensitive to vascular cognitive impairment and has been validated in the Portuguese population, was applied to all participants.[20]

Monitoring Protocol

Evaluations were carried out in a dim-lighted room, with a temperature of around 20°C, in supine position, and with bed head at 0°. Subjects were refrained from taking caffeine, alcohol, exercise, or vasoactive drugs for at least 12 hours before monitorization. Cerebral blood flow velocity (CBFV) was recorded bilaterally from the M1 segment of the middle cerebral artery (MCA), at a depth of 50-55 mm, with 2-MHz monitoring probes secured with a headband (Doppler-Box X, DWL, Singen, Germany). Continuous ABP was recorded with Finometer MIDI (FMS, Amsterdam, Netherlands) on the nondominant side. Heart rate (HR) was assessed from lead II of a standard 3-lead electrocardiogram. End-tidal carbon dioxide ($EtCO_2$) was recorded by nasal cannula with capnograph (RespSense, Nonin, Amsterdam, Netherlands). All data were synchronized and digitized at 400 Hz with PowerLab (AD Instruments, Oxford, UK) and stored for offline analysis. After resting for 20 minutes, a 10-minute period of resting data was stored for CA calculations. Afterwards, VMR and NVC protocols were performed.

Vasomotor Reactivity Protocol

After resting, subjects inspired a gas mixture of 5% CO_2, 21% O_2, and balance nitrogen for 2 minutes. After stabilization of hemodynamic parameters back to baseline, they hyperventilated to an $EtCO_2$ ~20 mm Hg for another 2 minutes. VMR is calculated as the slope of the relationship between $EtCO_2$ plotted against relative mean CBFV at the last 30 seconds of hypocapnia or hypercapnia and expressed as change % of the mean CBFV/mm Hg CO_2. VMR was also calculated separately for hypercapnia and hypocapnia.

Neurovascular Coupling Protocol

N-Back Task was performed and analyzed as by Sorond et al.[10] While in supine position, a sequence of single letters was displayed onto the ceiling. Subjects were instructed to press the mouse button each time a letter was repeated (1-Back) or each time a letter was repeated every other letter (2-Back). A control task was performed before each task—"Identify the letter X"; NVC was calculated as the ratio of the relative CBFV increase during the N-Back (CBFVNB) compared with the control task of "Identify the letter X" (CBFVIDX) using the following formula: $[(CBFVNB - CBFVIDX) / (CBFVIDX)] \times 100$.

Data Analysis and CA Calculations

For each heartbeat, the systolic, mean, and diastolic values of ABP and CBFV were calculated. Cerebrovascular resistance index (CVRi) was computed as the mean ABP / mean CBFV. Dynamic CA was assessed by transfer function analysis (TFA), which was done by calculating the coherence, gain, and phase parameters from beat-to-beat