ARTÍCULO ORIGINAL

El Posicionamiento Elevado de Cabeza y Cuerpo Podrían Afectar la Autorregulación Cerebral Dinámica en Pacientes con Enfermedad Silente de Pequeño Vaso Cerebral. Protocolo y Definiciones Operacionales.

Head-Up And Body Positioning Might Impair Dynamic Cerebral Autoregulation In Patients With Silent Cerebral Small Vessel Disease. Protocol And Operational Definitions.

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Resumen

Antecedentes: La autorregulación cerebral (CA) es la capacidad de los vasos cerebrales de mantener un flujo sanguíneo constante durante cambios en la presión de perfusión cerebral (PPC) relacionados con fluctuaciones de la presión arterial, cambios posturales o aumento de las demandas metabólicas. Se ha sugerido que las personas con enfermedad de pequeño vaso cerebral pueden tener CA deteriorada, pero la información no es concluyente. Describimos el protocolo de un estudio cuyo objetivo es evaluar la asociación entre hiperintensidades de substancia blanca y CA dinámica deficiente, para determinar los efectos del posicionamiento de cabeza y cuerpo en estos pacientes. **Métodos**: Utilizando un diseño de caso-control, evaluaremos la relación entre la severidad de las hiperintensidades de substancia blanca y la CA dinámica, mediante Doppler transcraneal continuo de las velocidades de flujo en las arterias cerebrales medias (ACM) combinadas con monitoreo de la presión arterial. La CA dinámica se analizará calculando el índice de flujo medio y la relación entre la presión arterial media y las velocidades medias de flujo de las ACM. Los participantes se clasificarán como casos si la IRM muestra hiperintensidades de substancia blanca. Para cada caso, se seleccionará a un individuo sin evidencia de enfermedad de pequeño vaso como control. **Comentario**: Este estudio evaluará si el posicionamiento de la cabeza hacia arriba afecta la CA dinámica en el contexto del daño subcortical difuso relacionado con enfermedad de pequeño vaso, proporcionando evidencia adicional sobre la importancia de la PPC en el mantenimiento del flujo en estos sujetos. El estudio proporcionará evidencia sobre el uso de terapia hipertensiva agresiva o intervenciones que promueven la hipotensión ortostática para reducir el riesgo de daño cerebral isquémico.

Palabras clave: Enfermedad de pequeño vaso; hiperintensidades de sustancia blanca; autoregulación cerebral dinámica; estudio poblacional.

Abstract

Background: Cerebral autoregulation (CA) is the ability of intracranial vessels to maintain a constant cerebral blood flow (CBF) during changes of cerebral perfusion pressure (CPP) related to fluctuations in blood pressure, postural changes or increased metabolic demands. It has been suggested that individuals with silent cerebral small vessel disease (SVD) may have impaired CA, but information is inconclusive. We describe the protocol of a study aimed to assess the association between white matter hyperintensities (WMH) of presumed vascular origin and poor dynamic CA, and to determine the effects of head-up and body positioning in patients with this condition. **Methods**: Using a case-control study design, we will assess the relationship between severity of WMH and dynamic CA, measured by continuous transcranial Doppler assessment of CBF velocities in the middle cerebral arteries (MCAs) combined with beat-to-beat blood pressure monitoring. Dynamic CA will be analyzed by calculating the mean flow index as the ratio of median arterial pressure and mean flow velocities of the MCAs. Participants will be categorized as case-patients if the MRI shows moderate-to-severe WMH. For every case-patient, an age- and sex-matched healthy individual with no neuroimaging evidence of SVD will be selected as a control. **Comment**: This study will assess whether head-up and body positioning impairs dynamic CA in the setting of diffuse subcortical damage related to SVD, providing further evidence on the importance of CPP in maintaining the CBF. If positive, the study will provide evidence favoring the stop of aggressive hypertensive therapy or interventions promoting orthostatic hypotension to reduce the risk of further ischemic brain damage in these cases.

Keywords: Small vessel disease; White matter hyperintensities; Dynamic cerebral autoregulation; Population-based study.

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Introduction

Cerebral autoregulation (CA) is defined as the inherent ability of the intracranial vasculature to maintain a constant cerebral blood flow (CBF) during changes of cerebral perfusion pressure (CPP) related to fluctuations in blood pressure (BP), postural changes or increased metabolic demands.[1] Conditions affecting the diameter of major intra or extracranial arteries are associated with impaired CA.[2] Indeed, patients with ischemic stroke in the territory of major intracranial arteries have been shown to have impaired CA, particularly in the cerebral hemisphere ipsilateral to the infarct.[3-5]

A growing body of evidence also suggests that individuals with lacunar infarctions or even those with silent neuroimaging signatures of small vessel disease (SVD), may have impaired CA; in these cases, CA has often been shown to be impaired bilaterally, suggesting a diffuse process.[6-11] However, the information is inconsistent as some studies failed to document such association.[12,13] Discrepancies could have been related to methodological issues or to differences in study designs. Moreover, some studies have calculated static CA while other have focused on dynamic CA, which is a more reliable approach to evaluate integrity of this adaptive mechanism in the setting of ischemic brain damage.[14]

To better evaluate impairment of dynamic CA in patients with diffuse cerebral SVD, some studies have assessed cerebral vasoreactivity in response to vasoactive drugs or to induced variations in PaCO2.[6,12] Head-up positioning has shown to reduce the CBF,[15] and can be used as a physiological approach to assess dynamic CA impairment. However, this method has not been well evaluated in patients with diffuse cerebral SVD.[16] Here, we present the protocol and operational definitions of a study aimed to assess the association between the presence of white matter hyperintensities (WMH) of presumed vascular origin (used as a surrogate of cerebral SVD) and poor dynamic CA, and to determine the effects of head-up and body positioning in patients with this condition.

Methods

Study Population: Atahualpa is a rural village located in coastal Ecuador, where previous epidemiological studies have been conducted. Methodology, operational definitions and ethics considerations of the Atahualpa Project have been described elsewhere.[17] In brief, Atahualpa residents who signed the informed consent have been enrolled in a population-based, prospective cohort study designed to reduce the increasing burden of non-communicable neurological and cardiovascular disorders in the region.[18]

Study design: Community-dwelling older adults (≥60 years) participating in the neuroimaging substudy of the Atahualpa Project[19-21] are considered eligible, and those who fulfilled inclusion criteria will be enrolled in the present study. These include: a clinical stroke-free status, no imaging evidence of hemorrhagic or ischemic strokes (with the exception of old silent lacunar infarcts), no significant (≥50%) stenosis of major intracranial arteries (on MRA) or extracranial vessels (on Doppler examination), no structural heart disease, sick sinus syndrome, intraventricular conduction disturbance or atrial fibrillation (assessed by means of a transthoracic echocardiogram and 24-hour Holter monitoring), and no clinical evidence of chronic obstructive lung disease, diabetic neuropathy, cirrhosis or traumatic brain injury (Table 1). Using a case-control study design, we will assess the relationship between severity of WMH and dynamic CA, measured by continuous TCD assessment of CBF velocities in the middle cerebral arteries (MCAs) combined with beat-to-beat blood pressure (BP) monitoring. Participants will be categorized as case-patients if the MRI shows moderate-to-severe WMH according to the modified Fazekas scale.[22] For every case-patient, an age- and sex-matched healthy individual with no neuroimaging evidence of SVD will be selected as a control. The protocol and the written informed consent are approved by the I.R.B. of Hospital-Clínica Kennedy, Guayaquil, Ecuador (FWA 00006867).

Table 1. Criteria for inclusion of participants of this study.

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Clinical stroke-free status.
No evidence of hemorrhagic or ischemic strokes (with the exception of old lacunar infarcts) on MRI.
No significant (≥50%) stenosis of major intracranial arteries on MRA or extracranial vessels on Doppler examination.
No structural heart disease, sick sinus syndrome, intraventricular conduction disturbance or atrial fibrillation (assessed by means of a transthoracic echocardiogram and 24-Holter monitoring).
No clinical evidence of chronic obstructive lung disease, diabetic neuropathy, cirrhosis or traumatic brain injury.

Dynamic cerebral autoregulation assessment: Potential participants will be instructed to avoid caffeine-containing products, nicotine, and alcohol for at least 12 hours before the test. Subjects will also be breathalyzed to ensure a blood alcohol content reading of 0.0%. Individuals taking sedatives, alpha or beta blockers, calcium channel blockers, anti-arrhythmic agents and tricyclic antidepressants will be excluded. In addition, all participants will be examined to rule out conditions that interfere with CA, such as orthostatic intolerance, orthostatic hypotension or the postural orthostatic tachycardia syndrome.[23,24] Medical records will be reviewed to get information on the presence of cardiovascular risk factors as described for the Atahualpa Project.[25]

Due to a previously documented high rate of insonation failures related to poor acoustic transtemporal win-

dows in Atahualpa residents;[26] potential participants will first undergo a regular TCD, following a well-known power motion mode Doppler/spectral TCD protocol;[27] and only those with at least one optimal transtemporal window (defined when flow signals could be measured for the mean, peak, and end-diastolic velocities of corresponding arteries) will be included for further analysis.

Continuous TCD assessment of CBF velocities in the MCAs and BP monitoring will be performed in a research center with subjects under comfortable room temperature. Operators will be blinded as to whether the individual has neuroimaging signatures or SVD (case-patient) or not (control subject). TCDs will be performed with the use of a SONARA portable transcranial Doppler system (VIASYS Healthcare, Inc. Madison, WI, USA) and two 2-MHz transducers secured to a head frame to prevent head movements during the study. BP monitoring (beat-to-beat changes in arterial pressure) will be performed with the use of a SOMNOtouch TM NIBP (SOMNOmedics, Randersacker, Germany) attached to the right middle finger.

After stable baselines levels are established, individuals will be monitored during 5 minutes in the supine position. Then, the head of the reclining examination table will be raised up to 45º and an additional 5-minute period in that position will be recorded for analysis. The subject will again be returned to the supine position for up to 5 minutes and then will be requested to stand up for an additional 5-minute continuous monitoring. End-tidal CO2 concentration values and respiratory frequency will be assessed by the use of an EMMA® Capnometer (Masimo Corporation; Irvine, CA, USA) over 1 minute at the beginning and end of each recording period (to assess modifications in these physiological parameters related to changes in head and body position).

Dynamic CA will be analyzed by calculating the mean flow index (Mx) as the ratio of median arterial pressure (MAP) and mean flow velocities of the MCAs (MCA Vmean). According to Reinhard et al,[28] mean values of both variables should be averaged over 3 seconds and, from every 20 such values (1 minute period), separate Pearson correlation coefficients between MAP and MCA Vmean will be calculated. For each of the monitoring periods (supine, after head-up mobilization and in the upright position), the five resulting sets of 1-minute correlation coefficients will be averaged, yielding three different autoregulatory Mx per subject. Correlation coefficient values close to zero indicate normal CA, whereas values closer to 1 or -1 suggested impaired CA.

Statistical analyses: All analyses will be carried out by using STATA version 14 (College Station, TX, USA). Descriptive statistics will be presented as means ± standard deviations for continuous variables and as percentages with 95% C.I. for categorical variables. Values of MCA Vmean, MAP, and correlation coefficients for each of the monitored periods will be compared across case-patients and controls. In addition, mean differences in these parameters according to head and body positioning will be independently assessed in case-patients and controls. These analyses will be carried out by the use of a linear model adjusted for cardiovascular risk factors. Predictive correlation coefficients score margins will be calculated for both case-patients and controls across supine, head-up mobilization and upright positions.

Table 2. Characteristics of case-patients and control subjects included in this study.

Characteristics	Case-patients (n=17)	Control subjects (n=17)	p value
Age, years (mean ± SD)	76.9 ± 7.3	75.6 ± 6.9	0.597
Women, n (%)	7 (41)	7 (41)	. . .
Current smoker, n (%)	0	0	. . .
Poor physical activity, n (%)	3 (18)	0	0.227
Poor diet, n (%)	1 (6)	0	. . .
BMI ≥30 kg/m2, n (%)	2 (12)	2 (12)	. . .
Blood pressure ≥ 140/90 mmHg, n (%)	10 (59)	7 (41)	0.494
Fasting glucose ≥ 126 mg/dL, n (%)	2 (12)	4 (24)	0.656
Total cholesterol ≥ 240 mg/dL, n (%)	5 (29)	3 (18)	0.688
Edentulism (<10 teeth), n (%)	11 (65)	6 (35)	0.169
MoCA score (mean ± SD)	17 ± 3.9	19.8 ± 2.8	0.028

Pre-Study Selection Of Participants

Of 351 Atahualpa residents aged ≥60 years enrolled in the neuroimaging substudy of the Atahualpa Project, 325 have been eligible to participate in this study (the others had died or declined further consent). Of these, 71 (22%) have moderate-to-severe WMH and have been investigated to determine whether they met the above-described inclusion criteria. Thirty of them qualified, of which 13 were further excluded because of absent transtemporal windows.

Therefore, the study will include 17 case patients with moderate-to-severe WMH and a similar number of age- and sex-matched control subjects. Table 1 summarizes the characteristics of case-patients and controls. There were no significant differences in demographics or cardiovascular risk factors across groups, although case-patients had a worse mean MoCA score than controls (Table 2). Besides having moderate-to-severe WMH,

cerebral microbleeds were noticed in six case-patients (35%) and silent lacunar infarcts in four (24%). As expected, these neuroimaging signatures of cerebral SVD were not observed in control subjects.

Comment

While pathophysiological mechanisms responsible for altered CA in these varied conditions are probably different, they have in common a reduced capability of cerebral blood vessels to adapt to changes of perfusion pressure related to fluctuations of arterial blood pressure, postural changes, or other imposed demands.

In the single study attempting to investigate the effects of heap-up positioning on dynamic CA in patients with diffuse subcortical damage of vascular origin, the authors found a greater reduction in the MCA Vmean after tilting in six patients with "leukoaraiosis" when compared to a similar number of controls (30.1% versus 5.5%, $p<0.001$).[15]

Major strengths of our study will include the unbiased selection of participants and the stringent inclusion criteria securing homogeneous characteristics of case-patients and their matched controls. However, the study have limitations. We will parallel changes in CBF velocities to changes in CBF, assuming that the cross-sectional areas of the insonated arteries will remained constant during data acquisition, which might not necessarily be true. In addition, we will compare average values of TCD Mx across groups and head positions as there are no definitive cutoff values to precisely detect lower an upper limits of normal CA. In conclusion, this study will assess whether head-up positioning impairs dynamic CA in the setting of diffuse subcortical damage related to SVD, providing further evidence on the importance of CPP in maintaining the CBF in these subjects. If positive, the study, will provide evidence favoring the stop of aggressive hypertensive therapy or interventions promoting orthostatic hypotension to reduce the risk of further ischemic brain damage in these cases.

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