Clinical Article

Brain lesion size and phase shift as an index of cerebral autoregulation in patients with severe head injury

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Summary

Background. Whether the phase relationship (phase shift) between cerebral blood flow velocity as assessed by transcranial Doppler ultrasound and blood pressure at 0.1 Hz can be used to assess cerebral autoregulation (CA) in patients with severe traumatic brain injury (TBI).

Methods. In 33 healthy volunteers (mean age, SD: 37 ± 17 years, range 17–65) middle cerebral artery (MCA) blood velocity (V) was recorded simultaneously with finger blood pressure (BP) over a period of 10 minutes under normocapnic and hypocapnic conditions to generate normative data. In 27 patients with severe TBI (Glasgow Coma scale score ≤8) serial close in time investigations of cranial computed tomography (CT) scanning and phase shift assessment were performed on days 1, 3, 5, and 8 after trauma. Phase shift in the MCA was compared to brain parenchyma lesion size in the MCA territory on CT scanning. Lesion size was classified into 0, normal; 1, presence of a small lesion (diameter < 3 cm); 2, presence of a large lesion (>3 cm).

Findings. Compared to normocapnia, hypocapnia significantly increased phase shift at 0.1 Hz from 78 ± 28° to 101 ± 25° (p < 0.001). In the TBI patients, 115 comparisons between CT findings and CA results were possible. Phase shift detected a pathological CA in 31 instances, which were more frequent in CT lesion type 2 (19/42) than in group 0 (7/44) and group 1 (5/29).

Interpretation. When CA is intended to be assessed by use of phase shift, the hyperventilation setting needs its own reference values. In MCA territories containing a traumatic lesion greater than 3 cm in diameter phase shift at 0.1 Hz will detect a high frequency (44%) of a disturbed state of CA.

Keywords: Cerebral autoregulation; head injury; transcranial Doppler ultrasound; transfer function.

Introduction

Cerebral autoregulation (CA) is the ability of the cerebrovascular system to provide a constant cerebral blood (CBF) flow supply to the brain in the presence of a mean arterial blood pressure (BP) between 50 and 150 mmHg. Using transcranial Doppler ultrasound the integrity of CA is usually assessed by a two point measuring method measuring blood flow velocity (V) at rest and after a challenge induced either by BP changes, by CO₂ or by Acetazolamide application as stressor [12, 17, 22]. Techniques referring to such two point measurements are called static methods to test CA. In recent years TCD has allowed the development of dynamic methods for this purpose due to TCD’s fast time resolution. These dynamic methods analyse the relationship between blood velocity changes and blood pressure changes by using either differential equations empirically [20, 21], or transfer function analysis [5, 15, 23], or a correlation index between V and BP at very long period length [4, 10]. Using transfer function analysis, some groups think of CA as a frequency dependent filter system in which the filtering process is expressed as phase shift between the real and the imaginary part of the complex transfer function between the corresponding frequencies in BP as input and V as output [5, 15, 23]. The exact reason of the frequency dependence [6] is not known, but CA can be considered a high-pass filter allowing passing through BP changes at high frequencies, but damping and delaying BP changes at low frequencies. A phase shift close to zero at frequencies which are usually damped can be interpreted as a loss of CA’s filter function, and hence a loss of CA.
It has been reported that the dynamic CA assessment methods and the static methods correlate [5, 10, 20, 23] prompting the assumption that the dynamic approach to assess CA could be clinically useful [4, 5, 14, 16]. We were interested in the relationship between brain lesion size and the frequency of CA disturbances using such a dynamic approach in patients with severe traumatic brain injury (TBI).

Material and methods

Normal subjects

With their written informed consent, 33 healthy subjects [male 20, female 13, mean age ± SD, 37 ± 13 years (range 14–62 years)] without any cerebrovascular risk factors or neurological diseases underwent simultaneous recordings of middle cerebral artery (MCA) blood flow velocity (Multi DopX4, DWL, Sipplingen, Germany, 2 MHz probe) and of BP at the finger tip (Ohmeda 2300 Finapres, Louisville, CO) using the TCD device ability to record both signals simultaneously. The volunteers were laying in a supine position. To measure end-tidal PaCO2 (Enhancer 3000xs, Diversified Diagnostic Products Inc., Houston, Tx) an anaesthetic facemask was placed and fixed in a comfortable way with rubber bands. Connected with the Enhancer 3000xs by short tubs room air was provided via the mask. Via a separate tube from the mask to the mask was provided via the mask. Via a separate tube from the mask to the Enhancer device end-tidal PaCO2 was measured. After fixing the mask and its connecting to the Enhancer device a transcranial Doppler probe holder provided by the manufacturer was applied. The fixations points of this probe holder consisting of light metal are both outer ear channels and the rim of the nose. Both MCAs were identified according to commonly accepted criteria and the TCD probes fixed on the probe holder when the best velocity signal was achieved. While the volunteers got comfortable to the setting the non-invasive blood pressure measuring device was mounted. Due to a poor temporal bone window on one side, in three volunteers only one MCA was investigated while in the remainder of the 30 subjects both MCAs were investigated, resulting in a total of 63 insonated arteries. When the subjects signalled that they were comfortable with the setting the recording of V and BP started. During the 10 minute recording period end-tidal PaCO2 values were collected every 20 seconds and summarized as a mean over the whole time period.

After 10 minutes the recording was stopped, and the volunteers were asked to breathe forcibly. When forced breathing and the fallen end-tidal PaCO2 had reached a steady state able to be maintained by the volunteers comfortably they were asked to maintain the intensity of forced breathing, and the recording of V and BP was started again for 10 minutes. The end-tidal PaCO2 values were again collected every 20 seconds and are reported as their mean over the whole time period of hyperventilation. Because hypoventilation is usually not used in the treatment of acute severe TBI we did not investigate hypercapnia.

TBI patients

All procedures to investigate the TBI patient were approved by the local ethics committee. We included 27 patients (male, 20; female, 7; mean age ± SD, 50 ± 20) with severe traumatic brain injury (Glasgow Coma Scale ≤8) [19] which were intended to be investigated repeatedly on days 1, 3, 5, and 8 after trauma using the same TCD device and the same probe holder. All patients had received a Spiegelberg-III-system which was used as an external ventricular drainage system, and also to measure intraventricular intracranial pressure (ICP). With the ICP known cerebral perfusion pressure as the difference between MAP and ICP was maintained above 70 mmHg using catecholamines when necessary. All patients received regular cranial computed tomography scan (CT) follow-ups within a short time frame with the TCD studies. The arterial line signal was fed into the TCD device for simultaneous recording of V and mean arterial BP; at the time of investigation the actual ICP was recorded and the actual PaCO2 was measured by blood gas analysis. The recording time ranged between 6 and 10 minutes. To compare the CA assessment results with the morphological CT findings we classified the brain parenchyma of each MCA territory into: 0, no lesion present; 1, presence of a small lesion: the summarized diameter of the lesion(s) is less than 3 cm; 2, presence of a large lesion: the summarized diameter of the lesion(s) is more than 3 cm. The diameter was measured using the cm scale adjacent on each CT scan image.

Data preparation

For all data analysis Matlab R12 (The MathWorks, Inc, Natick, MA) was used. The TCD device collects the input data with a frequency of 50 data points per second. We reduced the amount of data by averaging 100 data points to one new data point every 2 seconds (sampling frequency for data analysis 0.5 Hz providing a maximum frequency resolution of 0.25 Hz). The new data points were normalized to their means (e.g., (x-mean)/mean), and linear trends were removed by subtracting the straight line of best fit. All analyses were performed with these normalized and detrended data. A six minutes recording time is reduced approximately to 200 data points. To compare the recordings with a standard length of observation time we used the first 128 data points of each time sequence (corresponding to a time period of 256 seconds). Using fast Fourier Transformation (FFT) and rectangular windows the power spectra of BP (Gbpbp(f)) and V (Gvv(f)), and the cross-spectrum between BP and V (Gbpv(f)) were calculated from the 256 seconds period. The complex transfer function (TF(f)) is then estimated by

\[ TF(f) = Gbpv(f)/Gbpbp(f) \]

from which the phase spectrum and the phase shift at a given frequency can be extracted from the real and the imaginary part of TF(f). The used software calculates TF(f) to

\[ Y(t) = G(f) \times U(t) \]

which means that the output variable Y(t) (which is V) is modelled by the linear transfer function G applied to the input signal U(t) (which is BP). Because the phase shift at 0.1 Hz has been used previously for assessment of dynamic CA [5, 8, 9] we used the phase shift at this frequency for reasons of comparison with our results. A large positive phase shift between V and BP indicates that BP is delayed in comparison to V, a phase shift towards 0° indicates that V changes are coincident in time with the corresponding BP changes.

Statistical analysis

The data are reported as mean values and standard deviations (SD). In these normal subjects, the phase shift differences between normocapnia and hypocapnia were compared by paired t-test. To prove for age or sex effects linear regression analysis was used.

Results

Normal subjects

In the normocapnic setting end-tidal PaCO2 was 34 ± 3 mmHg and mean arterial BP 88 ± 9 mmHg. In the hypocapnic setting PaCO2 was lowered to 21 ± 3 mmHg while mean arterial BP remained constant.