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Cerebrovascular reactivity and cerebral autoregulation in normal subjects

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ABSTRACT

Background: Cerebrovascular reactivity (CVR) testing with CO2 challenge is used clinically as a measure of cerebrovascular reserve. However it is not known whether CVR measures the same physiological process as spontaneous cerebral autoregulation (CA).
Purpose: To compare CVR with CA in healthy volunteers, using continuous monitoring of cerebral blood flow velocity (CBFV) and arterial blood pressure (ABP).
Methods: We prospectively studied CVR and CA in 18 healthy volunteers. CVR was assessed using mean CBFV changes after 5% CO2 inhalation. CA was determined by transfer function analysis to derive the phase shift between spontaneous ABP and CBFV fluctuations at 0.1 Hz.
Results: CO2 inhalation produced a significant decrease in phase shift from $37.9 \pm 13.8°$ to $21.0 \pm 7.2°$ ($p<0.001$). In addition, there was a significant correlation between CVR and CA changes during CO2 inhalation ($R=-0.50, p=0.03$), but not between CVR and baseline CA ($R=0.22, p=0.4$).
Conclusion: We showed a decrease in spontaneous CA after vasodilatation. However, the lack of correlation between baseline CA and degree of CVR suggests that cerebrovascular reserve and CA are based in part on distinct physiological mechanisms. Further studies are needed to determine which of these parameters is most useful to guide treatment decisions in pathological states.

1. Introduction

Cerebrovascular reactivity (CVR) reflects the compensatory constrictive or dilatory capacity of distal cerebral arteries to a vasoactive stimulus. Using transcranial Doppler (TCD), CVR may be assessed using changes in mean blood flow velocity (mBFV) induced by CO2 inhalation [1], hypo- or hyperventilation [2,3], or injection of acetazolamide [4] . In clinical practice, impaired CVR, reflecting a reduced cerebrovascular reserve, predicts increased risk of ischemic stroke in patients with symptomatic and asymptomatic carotid artery disease [5–7] and predicts delayed cerebral ischemia after subarachnoid hemorrhage [8]. Whereas CVR is thought to be a marker of cerebral hemodynamic integrity, the underlying physiological process is cerebral autoregulation (CA), the brain's protective mechanism to maintain normal cerebral perfusion during fluctuations of arterial blood pressure (ABP). By continuously monitoring BFV and ABP, it is possible to quantify the continuous (or "dynamic") changes in CA directly, using a correlation coefficient [9], autoregulation index [10] or transfer function analysis [11].

Dynamic cerebral autoregulation (DCA) measurements, which have also been shown to predict ischemic risk [12], have certain advantages over CVR techniques in that they can be performed without the active cooperation of the patient (e.g. in comatose patients), and they do not require vasodilators that can increase intracranial pressure. If CVR could be shown to correlate highly with DCA, then the measurements of cerebral hemodynamic state could be assessed interchangeably with either technique. If, on the other hand, the methods are not concordant, then not only must the choice of methods be made based on the particular clinical situation, but the low amplitude, real-time autoregulation of blood flow may be considered a distinct physiological process from the response to a pharmacological challenge. In addition, because induced alterations in PCO2 are commonly used in management of cerebrovascular disease, it is important to characterize the effect of changes in CO2 on dynamic cerebral autoregulation.

One way to assess whether CVR and DCA measures correlate with one another is to quantify the changes in CA under the pharmacological challenge conditions of CVR, for example under CO2 inhalation. Conflicting results have been published regarding the impact of changes in partial pressure of CO2 on CA. Whereas several studies have shown a decrease in CA with increase in PaCO2 [13,14], a more recent study found no difference in CA with moderate increase in PaCO2 [15]. In this study, we sought to compare, in healthy volunteers, cerebrovascular reactivity with dynamic cerebral autoregulation determined with the transfer function analysis technique, using continuous monitoring of cerebral blood flow velocities and arterial blood pressure at baseline and under conditions of increased PCO2.

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2. Methods

2.1. Subjects

Eighteen healthy volunteers with no cerebrovascular risk factors were prospectively included in our study.

2.2. Data recording

Measurements were standardized with subjects in a supine position with upper body inclination of 30º. Data were collected in a quiet room with constant temperature. Patients were asked not to smoke or drink coffee during the 12 h before recording. A complete extracranial Duplex examination was performed in all patients to exclude any significant carotid artery stenosis or vertebral artery disease. Both MCAs were then located through the temporal windows at a depth of approximately 50–58 mm using 2 MHz probes (Terumo Trifid PMD150B, Spencer Technologies Seattle WA, USA), attached to a standard headframe to perform a continuous recording of CBFV waveforms. Arterial blood pressure waveform was continuously and non-invasively monitored using a finger cuff placed around the middle finger of the left hand (Finapres Pro, Finapres Medical Systems). Calibration was performed at the beginning of each recording using an inflatable arm cuff. Hydrostatic height correction was used to compensate for hand position. End-tidal CO2 (EtCO2) was measured continuously using an infrared capnometer (Normocap, Datex) connected to a facemask.

2.3. Intervention

During the entire procedure, ABP, CBFV and EtCO2 were continuously recorded. After 10 min of baseline recording during normal breathing (normocapnia), a mixture of air enriched with 5% CO2 was administered through the facemask, resulting in a progressive elevation of EtCO2 to a new plateau which was maintained for at least 10 min (hypercapnia).

2.4. Data analysis

2.4.1. Cerebrovascular reactivity

Cerbrovascular reactivity was calculated as % change in mean CBFV (mCBFV) per 1 mm increase in mean EtCO2 during CO2 inhalation (final):

$$CVR(\%) = 100x\frac{mCBFV(\text{final}) - mCBFV(\text{baseline})}{mCBFV(\text{baseline})} / (EtCO2(\text{final}) - EtCO2(\text{baseline}))$$

2.4.2. Cerebral autoregulation

ABP and CBF signals, sampled at 200 Hz during regular and CO2-breathing, were used for transfer function analysis in MATLab R12 (The MathWorks, Inc). Streams were clipped at their start and end to avoid transient, lead-in effects. Continuous data used for analysis averaged 4.8 (±0.6) minutes.

Spectral density was calculated for transfer function analysis using Welch's averaged periodogram method [11]. Baseline-subtracted streams were windowed with a 4000-point Hanning filter window with 50% overlap. From ABP and CBF signals, the auto-spectra Pabpabp (f) and Pcbfcbf(f), and the cross-spectrum Pabpcbf(f), were calculated for each frequency, f. The squared coherence function, $\gamma^2(f)$ was calculated as $\gamma^2(f) = |\text{Pabpcbf}(f)|^2 / (\text{Pabp}(f)\text{Pcbf}(f))$. The phase shift, $\varphi(f)$, was calculated from the real and imaginary parts of the cross-spectrum Pabpcbf(f) as $\varphi(f) = \arctan(Re(\text{Pabpcbf}(f))/Im(\text{Pabpcbf}(f))$. We reported the coherence and phase shift (in degrees) at 0.1 Hz, as it is at this frequency that a physiological, spontaneous oscillation of ABP occurs due to oscillations in autonomic system tone [16].

As phase shift values are only valid when the $\gamma^2(f)$ estimate differs significantly from zero, we calculated the significance of coherence at 0.1 Hz for each subject [17], and retained only those phase values for which the coherence was significant at $p<0.05$. Significant coherence values ranged from 0.08 to 0.15.

2.5. Statistical analysis

CA at baseline and during CO2 were obtained for both sides and averaged for statistical analysis. To determine the effect of CO2 challenge on CA, we calculated the change in phase shift between baseline and CO2 inhalation, referred to as *Cerebral Autoregulation Reactivity (CAR)*.

Cerebral autoregulation reactivity (CAR) was defined as the % of changes in CA phase shift per increase of 1 mm Hg in EtCO2 using the following equation:

$$CAR(\%) = 100x\frac{CA(\text{final}) - CA(\text{baseline})}{CA(\text{baseline})} / (EtCO2(\text{final}) - EtCO2(\text{baseline}))$$

We then investigated the correlation between the baseline CA (phase shift) and CVR and between CAR and CVR using a Pearson correlation coefficient. Our reasoning was that if CVR could be shown to be highly correlated with CA at baseline and under vasodilatory stimulation across individual subjects, then this would indicate that the two measures of cerebral hemodynamic status shared common physiological mechanisms—that is that the factors that determined the range of vasodilatory capacity (CVR) were the same that determined the degree of autoregulation under baseline and vasodilatory challenge. If the two were not correlated this would suggest that separate mechanisms were responsible for the 2 processes. SPSS 15.0 package was used for statistical analysis.

3. Results

Overall, there were 3 women and 15 men. The mean age was 32 ± 8 years.

3.1. Baseline physiological variables (Table 1)

At baseline mean phase shift was between 37.8 ± 13.8º. The mean ABP was 91.4 ± 10.6 and the mean CBFV was 45.4 ± 11.2 cm/s. Mean EtCO2 was 41.0 ± 3.8 mm Hg.

3.2. Effect of CO2 on physiological parameters

During CO2 challenge, we achieved an increase in EtCO2 from 41.0 ± 3.8 to 51.6 ± 3.9. This elevation was associated with a significant increase in mean CBFV from 45.4 ± 11.2 to 58.5 ± 16.3 and mean decrease in phase shift from 37.8 ± 13.8° to 21.0 ± 7.2° ($p<.001$, see Fig. 1). Additionally, the mean arterial blood pressure slightly increased from 91.4 ± 10.6 mm Hg to 93.7 ± 12.8 mm Hg ($p=0.04$). The mean CVR was calculated as 2.7 ± 1.2% increase in mean CBFV per 1 mm Hg and the mean CAR was −3.6 ± 3.4% decrease in phase shift per 1 mm Hg PCO2.

Table 1
Baseline characteristics of the 18 normal subjects.

Age	32	±8
Gender, Male	15	83%
Mean arterial pressure, mm Hg	91.4	±10.6
Mean blood flow velocity, cm/s	45.4	±11.2
Mean phase shift, °	37.9	±13.8
EtCO2, mm Hg	41.0	±3.8