CO₂ Reactivity Testing Without Blood Pressure Monitoring?

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Background and Purpose—Responsiveness to CO₂ is an established test of cerebrovascular reserve capacity. Arterial partial pressure of CO₂ (PaCO₂) and arterial blood pressure (BP) are key parameters for cerebral blood flow. To investigate the interaction between PaCO₂ and BP, we performed a study with simultaneous measurement of CO₂ and BP during CO₂ reactivity testing with transcranial Doppler sonography.

Methods—Eighty-one healthy volunteers, aged 19 to 74 years, underwent examination defined by a protocol with multimodality monitoring of BP, heart rate (HR), PaCO₂, and Doppler frequencies (DFs) of the left middle cerebral artery (MCA). Reproducibility was tested in a subgroup of 14 volunteers ≥65 years of age by CO₂ reactivity testing on different days.

Results—Increase of PaCO₂ was accompanied by a parallel increase of mean±SD time values of DF (3.6±1.6%/mm Hg CO₂). BP levels were significantly elevated after 60-second hypercapnia (mean values, 0.5±0.55 mm Hg/mm Hg CO₂). A significant decrease over time was seen only for pulsatility in DF but not in BP. Analysis of variance and covariance with repeated measures revealed a highly significant effect of CO₂ on MCA Doppler shift. A less-pronounced effect on DF was seen for BP. Correlation analysis showed no significance for CO₂ reactivity, but a significant correlation between test and retest was seen in BP-related CO₂ reactivity.

Conclusions—The CO₂ response curve showed the known linear increase of DF. The parallel significant increase in BP most likely results from activation of the central sympathetic nervous system. The poor reproducibility for Doppler CO₂ reactivity is to some extent explainable by variability of BP. CO₂-induced increases in BP can have relevant influence on MCA Doppler shift and lead to misinterpretation of Doppler CO₂ test results. (Stroke. 1999;30:398-401.)

Key Words: blood pressure ■ carbon dioxide ■ Doppler effect ■ ultrasonography, Doppler, transcranial

Cerebral blood flow (CBF) autoregulation and the arterial partial pressure of carbon dioxide (PaCO₂) have predominant influence on the regulation of global cerebral perfusion. Cerebral vessels constrict and dilate during increase and decrease of perfusion pressure. Myogenic (intrinsic response of vascular muscle to changes in stretch) and metabolic (release of mediators during tissue hypoxia) mechanisms have been proposed as important regulatory control systems.

The potent effect of CO₂ is a local action on cerebral arterioles and appears to be mediated by extracellular H⁺ ions. Therefore, cerebrovascular reserve capacity is tested by inducing changes in extracellular H⁺ ions (CO₂ reactivity or Diamox test).

In occlusive cerebrovascular disease, not only may responsiveness to changes in extracellular pH be deranged, but CBF autoregulation may also be impaired. After cerebral ischemia, tissue becomes pressure dependent owing to loss of CBF autoregulation.

CO₂ reactivity testing presupposes stable blood pressure (BP). Persistent slow and rapid changes in BP interfere with measurements of flow velocity in the MCA because of delay in autoregulatory response.

This study included simultaneous measurement of CO₂ and BP to assess the role of BP variability during CO₂ reactivity testing with transcranial Doppler sonography.

Subjects and Methods

Transcranial Doppler frequencies (DFs) under normocapnia and hypercapnia correspond closely to other cerebral blood flow measurements, accurately reflecting the relative changes in CBF during dynamic cerebral autoregulation measurements. Noninvasive continuous measurement of arterial BP by the Finapres method allows accurate measurement with a maximal variation of ±5 mm Hg, which is also representative for the brachial BP. End-tidal partial pressure of carbon dioxide (PETCO₂) and intra-arterial CO₂ were shown to correlate closely. PETCO₂ was measured in millimeters of mercury during expiration by an infrared capnometer with a probe attached to 1 nostril.

Eighty-one healthy volunteers, aged 19 to 74 years, underwent examination defined by a protocol with continuous measurement of digital BP and heart rate (HR) (Finapres), unilateral DF of the middle cerebral artery (MCA; EME TC2–64), and PETCO₂ (infrared capnometer, Normocap, DATEX). For analysis of reproducibility, an additional group of 14 volunteers, aged ≥65 years (range, 65 to 82 years) and without ipsilateral relevant atherosclerosis, was examined twice with the same protocol.

After a resting period of sufficient length to obtain stable baseline values, with the patients in supine position, a CO₂ reactivity test was performed twice with the same protocol.

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performed with rebreathing in a 50-L bag filled with 7% CO₂-enriched air.

Five phases were defined during CO₂ reactivity testing: baseline (phase 0) and the increase of PetCO₂ divided into steps of approximately 4 mm Hg CO₂ during rebreathing (phase I, beginning; phase II, 4 to 5 mm Hg CO₂; phase III, 8 to 9 mm Hg CO₂; and phase IV, 12 to 13 mm Hg).

The changes in DF were calculated as percentage of baseline values and the remaining parameters as differences from baseline. Data were reported as mean ± SD.

Data evaluation was carried out by standard statistical techniques (nonparametric Mann-Whitney test and nonparametric Wilcoxon’s test for paired samples). Analysis of variance and covariance with repeated measures were performed to investigate the interaction between the parameters measured. Spearman correlation coefficients were calculated for estimation of retest variability.

Results
Increasing PaCO₂ during CO₂ reactivity testing provoked a significant increase in DF. The time-mean of DF increased by 3.6 ± 1.6%/mm Hg CO₂ (P < 0.001), and pulsatility measured by Gosling’s pulsatility index decreased significantly after reaching 8 mm Hg PaCO₂.

During hypercapnia mean BP values increased significantly (see upper panel of Figure 1); mean values of BP were positively correlated to PetCO₂ (0.55 ± 0.50 mm Hg/mm Hg CO₂, P < 0.001). HR (not shown in Figure 1) was significantly elevated by 4.6 ± 7.8 bpm only during phase 4 (P < 0.01).

ANOVA with repeated measures showed that CO₂ as independent variable was the most relevant parameter for the variable MCA-DF but interacted closely with the covariables BP and HR.

A significant correlation was found between the covariables CO₂ (P < 0.001), BP (P < 0.05), and HR (P < 0.01). Multifactor variance analysis revealed that CO₂ was not the only relevant covariable.

The retest variability of 14 volunteers was quantified with Spearman correlation coefficients. The time-mean values of all measured parameters did show significant correlation (DF, 0.67, P < 0.01; BP, 0.66, P < 0.05; and CO₂, 0.70, P < 0.01), but CO₂ reactivity itself showed only a poor correlation (0.36, P = 0.20).

The correlation analysis for the BP-related CO₂ reactivity (CO₂ reactivity per mm Hg change in BP) revealed a significant Spearman correlation coefficient (0.73, P < 0.01).

Not only could the reproducibility be increased by additional BP measurements, but the interpretation of individual results of CO₂ reactivity testing could also be improved as shown in following cases.

In the first case, that of a 53-year-old migraineur, breath-dependent oscillations of BP induced amplified amplitudes of oscillation of DF under normocapnia. During hypercapnia, a significant increase of BP occurred, and changes in BP predominantly determined changes in DF. Steady-state hypercapnia was reached after 20 seconds and induced continuous increase of MCA blood flow velocity and BP over a period of 40 seconds. The relevance of changes in BP are plainly recognizable at the end of hypercapnia. Rapid changes due to arrhythmia led to parallel changes in DF (see Figure 2). This demonstrates that BP oscillations may interfere with CO₂ reactivity testing and result in limited reproducibility, even under physiological conditions in healthy people.

In the second case, a 69-year-old man presented with symptomatic high-grade carotid stenosis on the left side. The preoperative CO₂ reactivity testing is shown in Figure 3. No side-to-side differences were seen under normocapnia. A relevant increase of DF during hypercapnia on the left side was not observed. Vasomotor reactivity was exhausted on the left side. The MCA-DF, however, increased with the rise of BP at the end. CO₂ reactivity at the beginning of steady-state hypercapnia was 0%/mm Hg CO₂ and increased as a result of BP increase by 0.8%/mm Hg CO₂. Therefore, despite maximal vasodilatation, a falsely indicated partially maintained CO₂ reactivity was evoked by a CO₂-induced increase of BP.

Discussion
The CO₂ response curve confirmed the known linear correlation between PaCO₂ and MCA flow velocity.7–10,21 Recently, Kastrup et al22 observed an increase of BP during hypercapnia that reached values similar to ours but did not reach significance in the t test. The parallel increase of BP more than HR is induced by activation of the central sympathetic nervous system.23 In some individuals the effect of BP...
Figure 3. Patient with 90% stenosis of the left internal carotid artery with multimodality monitoring during CO₂ reactivity test: hypercapnia demonstrates exhausted vasomotor reactivity. Significant increase of MCA-DF on the left side is not visible despite hypercapnia (compare first and second bars that indicate periods of measurements). MCA-DF did not increase, however, until BP rose (third bar). Calculation of CO₂ reactivity revealed 0%/mm Hg CO₂ at the beginning of hypercapnic steady state. CO₂ reactivity increased at the end of hypercapnia because of BP increase from 0% to 0.8%/mm Hg CO₂ (see text for further details).

Figure 2. Individual multimodality monitoring during CO₂ reactivity testing in a 53-year-old migraineur with simultaneously recorded BP (in mm Hg), bilateral MCA flow velocity (mean time of MCA velocity in cm/s), and PetCO₂ (in mm Hg). See text for further details.
reaches the level of CO₂-induced changes. The differentiation of normal from pathological findings can be difficult because of large SDs of changes in BP and CO₂ during CO₂ reactivity testing (Figure 1). Therefore, the common Doppler CO₂ test should be interpreted very carefully, as recommended by Widder et al. In their opinion, only exhausted CO₂ reactivity is a significant finding. The problem of variable CO₂ effects on DF and BP can lead to misinterpretation of CO₂ test results if not all relevant parameters are monitored (see Figures 2 and 3). The effect of BP on MCA Doppler shift is not linear. This might be explained by the high-pass filter properties of cerebral autoregulation. Depending on the frequency of BP oscillation, a phase displacement and potentially a rise of amplitudes of DF oscillation was observed by Diehl et al. Therefore, simple mathematical methods are not able to extract the irregular variations in DF due to BP variations. In the present study, only individual phase-related data exist, with no opportunity of performing time-series analysis to exclude the individual effect of BP on CO₂ reactivity. An ongoing study of BP increase during CO₂ reactivity measurements in patients with carotid stenoses will provide such data. Parallel measurement of BP increases the individual reliability of CO₂ reactivity testing. Correlation of test and retest of CO₂ reactivity related to BP changes showed a moderately significant correlation, whereas the correlation of the Doppler CO₂ test alone was poor. We conclude that the consideration of changes in BP improves the prognostic value and minimizes false-negative results of CO₂ reactivity testing.

References
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