Intensive Care Med (2000) 26: 729–732

ORIGINAL

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Cerebral CO_2 vasoreactivity evaluation by transcranial Doppler ultrasound technique: a standardized methodology

Received: 26 May 1999
Final revision received: 14 February 2000
Accepted: 16 March 2000

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Abstract *Objective*: In normal subjects cerebral CO_2 vasoreactivity is measured during spontaneous hyperventilation, breathholding, or adding CO_2 to inspiratory gases. The correlation between CO_2 and cerebral blood flow may, however, be invalidated by the effects of a modified respiratory pattern on venous return, sympathovagal balance, and cathecolamine release. Moreover, the duration of the test, usually not considered, may play an important role. This may justify the scattering of values found in literature. We evaluated a new standardized method for overcoming these confounding factors.
Design: Experimental.
Participants: Twenty-one healthy volunteers.
Methods: Subjects were connected through a mouthpiece to a mechanical ventilator set in the intermittent positive pressure ventilation mode. The ventilator was fed by two 40-l tanks, one of which contained 5 % CO_2. The inspiratory CO_2 concentration was varied at fixed time intervals from 0 % to 5 % without modifying ventilator settings. End-tidal CO_2 was measured at the mouthpiece. Mean blood velocity (V_m) and pulsatility index (PI) in the middle cerebral artery were measured by means of transcranial Doppler ultrasound.
Results: The test was easily applicable and well tolerated. No hemodynamic alterations were observed during the tests. The correlation between CO_2 and V_m was always linear and highly significant ($R^2 > 0.8$, $p < 0.0001$). A low intersubject variability was observed. No difference was found between the two hemispheres, nor between the sexes.
Conclusions: The strict standardization of the technique, avoiding hemodynamic interference, may explain the low intersubject variability. The value of this technique in ventilated neurosurgical patients is still speculative, but it might allow the collecting of valuable data together with a reduction in exposure to CO_2, and hence cerebral blood flow modifications.

Key words Cerebral CO_2 vasoreactivity · Transcranial Doppler · Normal subjects

Introduction

Cerebrovascular reactivity to CO_2 is commonly investigated by measuring changes in mean blood velocity (V_m) in middle cerebral artery by means of transcranial Doppler ultrasound (TCD). Hypocapnia is obtained by voluntary hyperventilation, while hypercapnia is induced adding CO_2 to inspiratory gases or by breath holding. TCD values are obtained after a steady state is reached. Surprisingly, no standardization of the method

has been reported, and a number of possible misleading factors should be considered. Interference with venous return, stress-induced release of cathecolamines [1] and sympathovagal dysregulation, due to modifications in respiratory pattern [2], may affect cerebral hemodynamics. Moreover, Ellingsen et al. [3] found after 10 min of sustained hypo or hypercapnia a progressive correction in cerebral blood flow (CBF) toward pretest levels. The CO_2–V_m correlation may thus be altered, and standardization of the duration of the test is needed. All of these factors may explain why "normal" cerebral CO_2 vasoreactivity varies from 2% to 5%/mm Hg pCO_2 between studies (Table 1).

In neurosurgical intensive care units, where patients are generally intubated, cerebrovascular reactivity to CO_2 is tested modifying ventilator settings, but still hemodynamic interference and sympathovagal dysregulation may be expected. We propose a technique that avoids hemodynamic and respiratory interference, and that can be used without substantial modifications in ventilated critical patients. We tested it on healthy volunteers to evaluate its feasibility and to obtain "normal" reference values. Additionally, we evaluated whether the Goslin pulsatility index [$PI = (V_{systolic}–V_{diastolic})/V_{mean}$], often neglected in the literature, better represents the dependent variable since it is closely correlated, at least theoretically, to changes in microvascular resistance.

Materials and methods

After obtaining informed consent, 21 healthy subjects (10 men, 11 women; mean age 32 ± 7 vs. 28 ± 5 years) were connected, while supine, to a ServoVentilator 900B (Siemens, Danvers, Mass., USA) through a mouthpiece, with a noseclip in place, and ventilated in the intermittent positive pressure ventilation mode. The ventilator was fed by two 40-l tanks, one containing 50% O_2 in N_2 and the other 50% O_2, 5% CO_2 in N_2. Alternating the gas mixer from "21%" to "100%" thus made it possible gradually to change the inspiratory concentration of CO_2 ($FiCO_2$) from 0% to 5% without modifying ventilation or FiO_2. Tidal volume was set at 15 ml/kg and respiratory rate at 10–15 bpm. End-tidal CO_2 ($ETCO_2$) was measured with an infrared CO_2 analyzer (5250 RGM, Omheda, Louisville, Colo., USA). TCD of the middle cerebral artery (TC2–64B, EME, Oberlingen, Germany) was continuously measured with the probe held in place by a rubber band. The side with the better signal was chosen.

After a short period (1 min) of stabilization at $FiCO_2 = 0\%$, with an end-point for $ETCO_2$ at 30 mm Hg, $FiCO_2$ was increased in steps of 1.25% every 2 min from 0% to 5%, without aiming at a steady state for $ETCO_2$. Mean blood velocity, PI, and $ETCO_2$ were recorded every 10 s. The total duration of the test was approximately 10 min, during which 60 sets of data were recorded for each subject. Pulse oximetry, noninvasive blood pressure, and heart rate were measured every 1 min.

Linear regression analysis was performed between $ETCO_2$ and V_m or PI. From the resulting equation, cerebral CO_2 vasoreactivity was calculated as the percentage change in V_m ($VMRV_m$) or PI (VMRPI) for mm Hg change in $ETCO_2$, assuming normal ET-CO_2 = 40 mm Hg. Three subjects had CO_2 reactivity evaluated on both hemispheres.

Data are presented as mean ± SD. The coefficient of variation was calculated to assess the variability in our set of measurements. Student's *t* test for unpaired data was used to compare groups (men vs. women).

Table 1 Cerebral CO_2 vasoreactivity in healthy subjects: mean values (CBF: vasoreactivity evaluated by CBF measurement, TCD: vasoreactivity evaluated by TCD)

Study	year	TCD/CBF	Cerebrovascular Reactivity to CO_2 (%/mm Hg^{1})
Kety and Schmidt [4]	1948	CBF	1.95
Olesen et al. [5]	1971	CBF	2.86
Ackerman et al. [6]	1973	CBF	2.66
Markwalder et al. [7]	1984	TCD	3.2
Bishop et al. [8]	1986	CBF	3.1
Leopold et al. [9]	1987	TCD	2.8
Ringelstein et al. [10]	1988	TCD	5
Ogawa et al. [11]	1988	TCD	4
Hassler and Chioffi [12]	1989	TCD	2.1[a]
Hassler and Chioffi [12]	1989	TCD	4.7[b]
Seiler and Nirkko [13]	1990	TCD	3.2
Fortune et al. [14]	1992	TCD	2.3
Klingelhofer and Sander [15]	1992	TCD	3.7
Eng et al. [16]	1992	TCD	3.2
mean			3.2

[a] values obtained during hypocapnia
[b] values obtained during hypercapnia

Table 2 Cerebral CO_2 vasoreactivity measured in 21 healthy subjects

Subject	Age yrs	Sex	$VMRV_m$ (%/mm Hg^{1})	r^2	VMRPI (%/mm Hg^{1})	r^2
1	23	M	3.52	0.967	–3.98	0.841
2	30	M	2.58	0.921	–3.43	0.835
3	35	M	2.78	0.902	–3.79	0.854
4	25	M	3.30	0.948	–3.23	0.682
5	28	F	3.28	0.958	–3.44	0.606
6	35	M	3.04	0.935	–2.93	0.837
7	41	M	2.21	0.904	–2.65	0.838
8	31	F	3.99	0.959	–4.44	0.807
9	33	M	2.64	0.962	–2.89	0.878
10	35	M	2.74	0.931	–2.90	0.893
11	33	F	2.47	0.927	–2.00	0.532
12	22	F	3.81	0.845	–1.68	0.236
13	25	F	3.49	0.963	–3.83	0.716
14	21	F	3.30	0.924	–4.13	0.757
15	25	F	2.38	0.936	–4.15	0.725
16	42	M	4.30	0.878	–3.79	0.766
17	29	M	3.53	0.935	–4.26	0.876
18	23	M	3.42	0.957	–5.95	0.733
19	25	F	3.19	0.881	–4.10	0.801
20	29	F	3.47	0.913	–2.34	0.498
21	37	F	3.65	0.980	–7.56	0.840
mean ± SD	30 ± 6		3.19 ± 0.55		–3.69 ± 1.30	

Table 3 Comparison of cerebral CO_2 reactivity in the two hemispheres in three subjects (dx: right hemisphere, sx: left hemisphere)

Subject	Age (yrs)	$VMRV_{mdx}$ (%/mm Hg^{1})	$VMRV_{msx}$ (%/mm Hg^{1})	$VMRPI_{dx}$ (%/mm Hg^{1})	$VMRPI_{sx}$ (%/mm Hg^{1})
5	28	3.28	3.33	–3.44	–4.05
7	41	2.21	2.62	–2.65	–2.35
9	33	2.64	2.61	–2.89	–3.23

Results

Baseline V_m and PI means were 60 ± 9 cm/s and 0.90 ± 0.11, respectively. $ETCO_2$ was increased by 15.3 ± 2.9 mm Hg (range 11–21) from the initial value of 30.0 ± 2.1 mm Hg. The response of V_m and PI to CO_2 changes was always linear. The correlation between $ETCO_2$ and V_m was highly significant ($p < 0.0001$), with R^2 always greater than 0.84 (Table 2). PI showed a lower but still significant correlation ($p < 0.0001$). $VMRV_m$ was 3.19 ± 0.55/mm Hg, with a low coefficient of variation (17.4). VMRPI showed a similar mean value (–3.69 ± 1.30/mm Hg) but a higher variability. $VMRV_m$ (3.10 ± 0.59 vs. 3.30 ± 0.53 %/mm Hg. n. s.) and VMRPI (–3.62 ± 0.93 vs. –3.77 ± 1.66 %/mm Hg, n. s.) were similar in women and men. Table 3 presents data obtained bilaterally in three subjects. Hemodynamic parameters and pulse oximetry were stable throughout the tests. Ventilation was reported as comfortable by all the subjects.

Discussion

Ventilation, and hence CO_2, is a potent means for manipulating cerebral perfusion. Hypocapnia decreases and hypercapnia increases the diameter of cerebral arterioles [17, 18]. The consequent change in vascular resistance modulates CBF. This response is very rapid [19]. The measurement of cerebral reactivity to CO_2 is used to assess the severity of brain damage and the outcome [15], provide guidelines for hyperventilation therapy [20], differentiate vasospasm from hyperemia [12], evaluate the possible beneficial effects of barbiturate and osmotic therapy [21, 22], and assess the risk of cerebral ischemia in patients with occlusive carotid artery disease [23, 24]. TCD is a widely accepted technique for noninvasively evaluating cerebrovascular reactivity since variations in V_m measured in the middle cerebral artery have been shown to be correlated with changes CBF [8, 25].

When testing cerebral CO_2 vasoreactivity in healthy, spontaneously breathing subjects, $PaCO_2$ is varied, modifying the respiratory pattern or adding CO_2 to inspiratory gases to achieve a hypercapnic state. However, changes in intrathoracic pressures may influence venous return and cardiac output, while the stress of voluntary hyperventilation may alter sympathetic discharge. It has also been shown that changes in respiratory frequency modify sympathovagal balance [2]. All these factors produce hemodynamic effects which endanger the validity of the $ETCO_2$/TCD (or CBF) correlation. Furthermore, a progressive normalization of CBF during a sustained modification of $PaCO_2$ has been demonstrated [3]. In ten normal subjects we found a 8.6 ± 7.4 % increase in V_m after 10 min of a sustained hypocapnia (unpublished data). Assuring stable intrathoracic pressure and respiratory rate, this test eliminates many possible confounding factors. It is easily applicable and reported by patients as being comfortable. A very good linear correlation between V_m and $ETCO_2$ has been found, based upon findings reported by Kirkham et al. [25] and Eng et al. [16] over a wide range of CO_2 values (20–60 mm Hg).

$VMRV_m$ was comparable to averaged data reported in the literature (Table 1). These data, however, range from 2 % to 5 %. It is reasonable to think that the differences in technique are responsible for this wide variation. The avoidance of hemodynamic interference may explain the low variability that we observed. VMRPI was comparable to $VMRV_m$ but showed greater variability. It has been demonstrated that the calculation of this parameter may be altered by modifications in the intensity of the signal [1] without changes in V_m readings. PI did not seem to offer any advantage over V_m in the description of CO_2 vasoreactivity, at least in normal subjects. No difference was found between men and women. The comparability between the two hemispheres was noteworthy.

The value of this technique in ICU patients is still speculative. However, it may offer many advantages: since ventilator settings do not have to be modified during the test, hemodynamic interference is avoided; comparison to "normal values" is not endangered by method-related artifacts; and the use of a "dynamic" test, i. e., without aiming at a steady-state for CO_2, allows a reduction in the time during which the patient is exposed to CO_2 modifications. This is essential in situations of severe brain damage, where any procedure which may alter cerebral perfusion should be minimized.

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