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AGE DEPENDENCY OF CEREBRAL OXYGENATION ASSESSED WITH NEAR INFRARED SPECTROSCOPY

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ABSTRACT

Near infrared spectroscopy (NIRS) is an optical technique that provides information on cerebral tissue oxygenation and hemodynamics on a continuous, direct, and noninvasive basis. It is used to determine cerebral blood volume (CBV) and cerebrovascular CO_2 reactivity during normoxic hyper- and hypocapnia in a group of 28 healthy volunteers aged 20 to 83 years. The main focus is on to the age dependency of the measured variables. The influence of changes in minute ventilation during normocapnia on the cerebral oxygenation was also studied. The mean CBV ($\pm$SD) in age was, for 20 to 30 years, 2.14 ± 0.51 ml/100 g of brain tissue; for 45 to 50 years, 1.92 ± 0.40 ml/100 g; and for 70 to 83 years, 1.47 ± 0.55 ml/100 g. The CBV showed a significant decrease with advancing age. No influence was found for a change in minute ventilation on cerebral oxygenation. During hypercapnia cerebral blood flow (CBF) significantly increased in all age groups, with a factor of 1.31 ± 0.17 kPa^{-1}, 1.64 ± 1.39 kPa^{-1}, and 2.4 ± 1.7 kPa^{-1}, respectively, for the three age groups. The difference in change among the age groups was not statistically significant ($p = 0.09$). The trend seen was an increased change in CBF with advancing age. During hypocapnia, the CBF significantly decreased in all age groups, with a factor of 0.89 ± 0.08 kPa^{-1}, 0.89 ± 0.04 kPa^{-1}, and 0.85 ± 0.11 kPa^{-1}, respectively. There was no significant difference among the age groups ($p = 0.50$). *© 1997 Society of Photo-Optical Instrumentation Engineers.* [S1083-3668(97)00902-7]

Keywords near infrared spectroscopy; cerebral oxygenation; hemodynamics; cerebral blood flow (CBF); cerebral blood volume (CBV).

1 INTRODUCTION

For the brain, arterial carbon dioxide tension ($PaCO_2$) is one of the strongest physiological modulators of cerebral vascular resistance (CVR); hypocapnia (hv) induces cerebral vasoconstriction whereas hypercapnia (hc) causes cerebral vasodilatation.[1–3] An increase in CVR results in a decrease of cerebral blood flow (CBF) and cerebral blood volume (CBV). A decrease in CVR will result in an increase in both CBV and CBF.[4,5] Measurement of CBF and CBV is important for investigating alterations in cerebral physiology that can occur as a result of, for example, pulmonary diseases or the effects of advancing age. Advanced methods such as magnetic resonance imaging and positron emission tomography (PET), or tracer methods such as ^{133}Xe clearance, have been developed to assess cerebral circulation. Although these methods provide adequate results, they have several disadvantages. All of them rely on sophisticated and expensive equipment that is not commonly available. Also, the patient must be transported to the instrument. In the case of ^{133}Xe clearance, a radioactive tracer is needed, making it invasive. A technique that does not have these disadvantages is transcranial Doppler sonography (TCD). This technique provides a measure for cerebrovascular CO_2 reactivity. We did not use this technique mainly for two reasons. First, it is not possible to find a suitable cranial window in all subjects and second, it does not provide information on the oxygenation of the cerebrum.

A relatively new technique for measuring cerebral oxygenation and hemodynamics is near-infrared spectroscopy (NIRS). This optical, noninvasive technique has none of the drawbacks mentioned earlier. In the past, NIRS has mainly been used to monitor cerebral functioning in neonates.[6,7] Recently the technique has also been employed on adults to assess circulatory variables.[8–11]

The CO_2 reactivity of the cerebral circulation of neonates[12] and young healthy adults[13] is well docu-

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mented. Wyatt et al.[12] studied CBV response to changes in $PaCO_2$ with increasing maturity in a group of infants. An increase in CBV during hypercapnia was found in preterm and term infants. These workers also found a marked increase in cerebrovascular response to changing $PaCO_2$ with increasing maturity. However, except for neonates, there is only minimal and controversial information about age-related changes in cerebrovascular CO_2 reactivity. Lassen, Munck, and Tottery,[14] Hachinski et al.,[15] and Simard et al.[16] described a normal CO_2 reactivity with advancing age. Gotoh, Meyer, and Takagi,[17] Schieve and Wilson,[18] Yamaguchi et al.,[19] Yamamoto et al.,[20] and Scheinberg et al.,[21] on the other hand, found a reduction in cerebrovascular CO_2 reactivity with advancing age.

This study therefore focuses on the effect of aging brain on CBV and on cerebrovascular CO_2 reactivity in healthy subjects of different ages. Main attention is given to subjects 70 years and older, who to the best of our knowledge have not yet been studied. Also, the influence of changes in minute ventilation during normocapnia on cerebral oxygenation is studied.

2 MATERIALS AND METHODS

2.1 SUBJECTS

Six healthy volunteers—4 female and 2 male (mean age 28 years, range 22 to 44 years)—participated in a study to determine the influence of minute changes in ventilation on cerebral oxygenation.

Twenty-eight healthy volunteers participated in the main study on age-dependent CO_2 reactivity. The subjects were divided into three groups. Group 1 consisted of young subjects (20 to 30 years), group 2 contained middle-aged subjects (45 to 70 years), and group 3 consisted of elderly subjects (70 years and over). None of the subjects were on medication. At least 2 h prior to the experiments, the subjects had to abstain from caffeinated drinks. All subjects gave informed consent after full explanation of the research protocol, which was approved by the medical ethical committee of the Universitary Lung Centre Dekkerswald and of the Radboud Hospital of the University of Nijmegen.

2.2 NIRS

In the past few years NIRS has become a more and more widely used noninvasive method for determining circulatory and hemodynamic variables. The technique relies on the relative transparency of human tissue to light in the near-infrared region and on the oxygenation-dependent absorption changes in cerebral tissue caused by chromophores—mainly oxy- and deoxyhemoglobin (O_2Hb and HHb). By measuring changes in light absorption at different wavelengths, tissue oxygenation can be monitored continuously. Owing to light scattering in the tissue, only changes in concentration in the chromophores from an arbitrary zero can be determined. A modified Lambert–Beer law[22] gives the relationship between the changes in concentration and absorption. A path-length factor is incorporated to account for the scattering of light in the tissue. In this study an age-dependent path-length factor ($4.99+0.067\times AGE^{0.814}$) was used.[23] The sum of O_2Hb and HHb (tHb) is a measure of the change in total blood volume in the tissue.

An absolute measure for CBV can be obtained by combining NIRS with pulse oximetry: if a small and gradual change in arterial saturation (SaO_2) is applied to a subject, the effect of that change on the cerebral circulation can be monitored with NIRS. An absolute change in SaO_2, measured with a pulse oximeter, can then be related to a relative change in concentration of O_2Hb. To avoid physiological changes in the cerebral circulation during the determination of the CBV, the change in SaO_2 should be small. This method of quantifying CBV was first described by Wyatt et al.[24] for neonatal applications. In adults the method has extensively been described by Elwell et al.[8,25]

A 4-wavelength, attenuation-type NIRS instrument (Radiometer Medical A/S, Copenhagen, Denmark) was used.[7,26] The distance of the NIRS optodes was 5.5 cm for all experiments. The NIRS data and other physiological data were collected every second, displayed in real time, and stored on disk for off-line analysis and calculation of CBV. The algorithm that was used to convert changes in absorption into changes in concentration is described elsewhere.[7,27]

2.3 DETERMINATION OF CBF

A change in CBF will result in changes in the concentration of O_2Hb and HHb. These changes, monitored with NIRS, were compared with the slope, in micromolar of O_2Hb per percent change of SaO_2, from the CBV data. Under the assumption that (small) changes detected in the arterial system with pulse oximetry occur equally throughout in the capillary and venous system, we can estimate the change in CBF during hypercapnia compared with normocapnia (nc):

$$\frac{CBF_{\mathrm{hc}}}{CBF_{\mathrm{nc}}} = \frac{\mathrm{SaO}_{2,\mathrm{nc}} - 65\%}{\mathrm{SaO}_{2,\mathrm{hc}} - 65\% - \Delta\mathrm{SjvO}_2},$$

where $CBF_{\mathrm{hc}}/CBF_{\mathrm{nc}}$ reflects the change in CBF (expressed as a dimensionless factor), $SaO_{2,nc}$ (in percent) is the arterial saturation during normocapnia, $SaO_{2,hc}$ (in percent) is the arterial oxygen saturation during the hypercapnic steady state, and $\Delta SjvO_2$ (in percent) is the change in jugular venous oxygen saturation caused by the increase of the accompanying arterial carbon dioxide tension, derived from the NIRS data. The 65% in the formula indicates the average jugular venous oxygen concentration in healthy subjects. The same calculation

holds for the hypocapnic steady state. In this case the hc indices in the formula have to be replaced by the index hv.

Not all subjects experience the same change in arterial carbon dioxide tension during either hyper- or hypocapnia. Therefore, to compare groups, the change in CBF has to be expressed as a percent change per kilopascal of change in arterial carbon dioxide tension. In this case the $\Delta SjvO_2$ also has to be expressed as a percent change per kilopascal. There are two assumptions to be made for this calculation to be valid. The first is that the oxygen uptake in the brain does not change during hyper- or hypocapnia.[28,29] The second is that the average jugular venous oxygen concentration in healthy subjects is 65%.[30,31] A more extensive derivation of this method is given in Appendix A.

2.4 PROTOCOL

2.4.1 Influence of Minute Ventilation on Cerebral Oxygenation

To determine the influence of changes in minute ventilation on cerebral oxygenation (O_2Hb, HHb, and tHb) during constant end-tidal tension CO_2 tension ($PetCO_2$), a ''dead-space test'' was performed. The subjects were connected to a spirometer (Lode Instruments, Groningen, The Netherlands) and minute ventilation was calculated from the spirogram. It was changed by increasing the dead space and by connecting tubes of different volume (75, 325, and 650 ml) between the mouthpiece and the spirometer. The $PetCO_2$ was continuously monitored with a combined pulse oximeter and capnograph (N1000, Nellcor Inc., U.S.). After a steady state was reached, data were recorded for 60 s. As a base level for the NIRS data, normal ventilation (without mouthpiece/spirometer) was used.

2.4.2 Age Dependency of Cerebrovascular CO_2 Reactivity

The subjects were placed in supine position, lying on a bed. The SaO_2 was measured with a pulse oximeter (N200, Nellcor Inc., U.S.). The sensor of the pulse oximeter was attached to the cheek of the subject to correct for temporal differences between cerebral and peripheral circulation. For safety reasons the sensor of a second pulse oximeter (N1000, Nellcor Inc., U.S.) was attached to the left index finger of the subject. For the same reason the ECG was monitored. The $PetCO_2$ and the respiration rate were monitored with a capnograph (N1000, Nellcor Inc., U.S.). The inspired oxygen fraction (F^IO_2) was measured with an oxygen analyzer (OM-11, Beckman Inc., U.S.). The subjects breathed in a closed spirometer system in which the O_2 and CO_2 concentrations could be controlled. During the experiment, arterialized blood samples were taken four times, after warming the hand in 40 °C water. Immediately after withdrawal of the sample, blood gases were analyzed on a blood gas analyser (IL 1312, Instrumentation Laboratory, Italy). The first sample was also analyzed on an oximeter (IL 482, Instrumentation Laboratory, Italy) to determine blood hemoglobin content, which is necessary for calculating CBV.

The protocol was divided into four stages. In the first stage, a normoxic and normocapnic period of steady state was monitored for 1 min. During the second stage, normocapnic hypoxia was induced by altering the F^IO_2 until an SaO_2 of approximately 90% was reached. From this short and transient desaturation, the CBV and the change in concentration of O_2Hb and HHb per percent decrease of SaO_2 was determined. The averages of two desaturations were taken. During the third stage (normoxia and hypercapnia), CO_2 was slowly added to the closed breathing circuit until the $PetCO_2$ was increased by approximately 1 kPa, followed by a 1-min steady-state period. During the fourth stage, the subjects were asked to hyperventilate at a frequency twice the breathing frequency at rest. The subjects were guided by a metronome. Visual feedback on the tidal volume was obtained directly from the spirometer in the closed breathing system. Hyperventilation was maintained at such a level that, after the $PetCO_2$ had decreased approximately 1 kPa, a 1-min steady-state period was possible. At the end of the 1-min steady-state periods of the first, third, and fourth stages, blood samples were taken from the finger.

2.4.3 Statistical Analysis

The data from the ''dead space test'' were analyzed using a paired Student t-test. For the study on the age dependency of cerebrovascular CO_2 reactivity, a one-way ANOVA was used. Spearman rank correlation was used to test for age dependency of CBV. For all tests, the significance level was set at $P<0.05$. The results are given as mean $\pm$SD.

3 RESULTS

3.1 INFLUENCE OF MINUTE VENTILATION ON CEREBRAL OXYGENATION

The minute ventilation examined in the ''dead space test'' ranged from 5 to 15 liters/min. No significant changes in concentration of O_2Hb, HHb, and tHb were found among the different levels of minute ventilation (Table 1).

3.2 AGE DEPENDENCY OF CEREBROVASCULAR CO_2 REACTIVITY

3.2.1 CBV

The individual values for CBV of all age groups are given in Table 2. The mean CBV in groups 1, 2, and 3 was 2.14 ± 0.51 ml/100 g, 1.92 ± 0.40 ml/100 g, and 1.47 ± 0.55 ml/100 g, respectively. The mean CBV of age group 3 was significantly lower than that of age group 1 ($p=0.02$). Figure 1 shows the

Table 1 Concentration changes (μM) of oxyhemoglobin, deoxyhemoglobin, and total hemoglobin as a result of a change in minute ventilation induced by changing the dead space volume (ml). The minute ventilation examined ranged from 5 to 15 liters/min. For the NIRS data, the change in concentration from minute ventilation without dead space (no mouthpiece/spirometer) was taken. No significant changes were found.

Dead space	O_2Hb	HHb	tHb
0→75	0.12	−0.11	−0.02
75→325	0.05	−0.08	−0.04
325→625	0.12	0.55	0.67

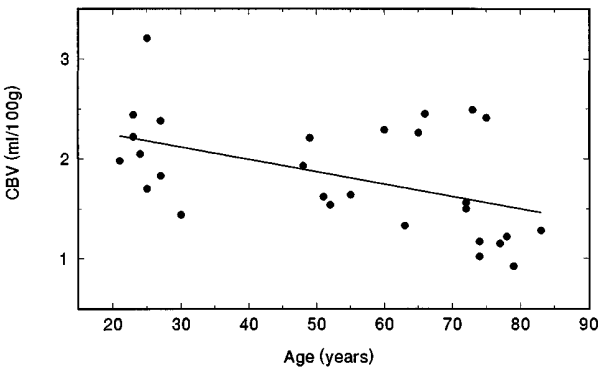

Fig. 1 Relationship between cerebral blood volume and age between 21 and 83 years for 28 subjects ($p<0.05$).

values of the CBV as a function of age for all 28 subjects. A significant decrease in CBV with advancing age of 0.012 ml/100 g/year was found ($p=0.01$).

3.2.2 Hypercapnia

The individual values for the change in minute ventilation due to hypercapnia for all age groups are given in Table 3. During hypercapnia, a significant increase in minute ventilation among the three groups was observed ($p=0.049$). The ventilatory response to the increase in $PaCO_2$ was smallest in group 3.

Table 4 gives the changes in concentration of O_2Hb, HHb, and tHb for all age groups during hypercapnia. The increase in tHb per kilopascal of change in $PaCO_2$ was significantly different among the groups: the change in tHb of group 1 was larger than the change in tHb of groups 2 ($p<0.001$) and 3 ($p<0.01$). The changes in O_2Hb and HHb among age groups were not significantly different.

The mean change in CBF, compared with normocapnia, for groups 1, 2, and 3 was a factor of 1.31 ± 0.17 kPa^{-1}, 1.64 ± 1.39 kPa^{-1}, and 2.4 ± 1.7 kPa^{-1}, respectively. The increase in CBF was significant for all groups. The difference in change among the age groups was not significant ($p=0.088$); however, it was observed that the change in CBF increased with advancing age.

3.2.3 Hypocapnia

A significant decrease in tHb was observed for all age groups. Among the groups, it was found that group 3 showed a significantly lower decrease of tHb than age group 2 ($p=0.02$), but not age

Table 2 Individual results of the mean cerebral blood volume (CBV) of two determinations (ml/100 g) for three age groups (age in years).

	Age group 1		Age group 2		Age group 3	
Subject	Age	CBV	Age	CBV	Age	CBV
1	21	1.98	63	1.33	77	1.15
2	27	1.83	55	1.64	73	2.49
3	24	2.05	66	2.45	78	1.22
4	30	1.44	60	2.29	79	0.92
5	23	2.44	49	2.21	74	1.17
6	23	2.22	52	1.54	74	1.02
7	25	3.21	65	2.26	72	1.56
8	27	2.38	48	1.93	75	2.41
9	25	1.70	51	1.62	83	1.28
10	-	-	-	-	72	1.50
Mean±SD	25±3	2.14±0.51	57±7	1.92±0.40	76±4	1.47±0.55

Table 3 Individual results of change in minute ventilation (liters/min/kPa) caused by hypercapnia.

Subject	Age group 1	Age group 2	Age group 3
1	10.1	4.0	10.2
2	14.6	15.7	4.9
3	11.5	23.8	9.3
4	1.1	20.0	13.3
5	14.4	7.4	1.3
6	2.8	14.2	11.4
7	5.8	14.5	−8.7
8	13.8	7.8	1.8
9	8.7	12.9	14.5
10	-	-	−0.1
Mean±SD	9.2±5.0	13.4±6.3	5.8±7.3

group 1 ($p=0.10$). The changes in O_2Hb and HHb among the age groups were not significantly different.

The mean change in CBF, compared with normocapnia, for groups 1, 2, and 3 was a factor of 0.89 ± 0.08 kPa^{-1}, 0.89 ± 0.04 kPa^{-1}, and 0.85 ± 0.11 kPa^{-1}, respectively. The decrease in CBF was significant for all groups, but was not significantly different among age groups ($P=0.50$). The relationship among individual changes in $PaCO_2$, for both hypo- and hypercapnia, and the change in CBF compared with normocapnia is shown in Figure 2.

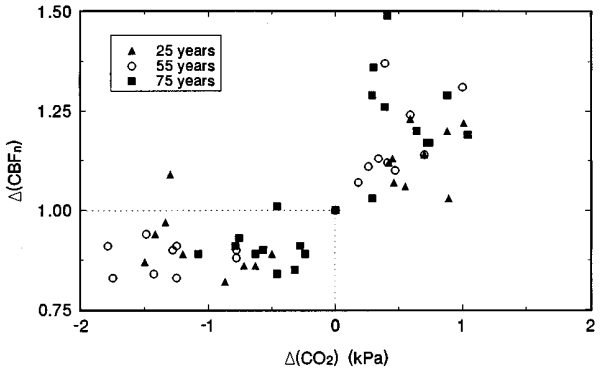

Fig. 2 Relationship between the change in cerebral blood flow compared with normoxia and the change in arterial CO_2 tension for all subjects ($n=28$). The arterial CO_2 tension during normocapnia is used as the reference value.

4 DISCUSSION

4.1 INFLUENCE OF MINUTE VENTILATION ON CEREBRAL OXYGENATION

By increasing the dead space of the mouthpiece and tube through which the subjects were breathing, we were able to change the minute ventilation but keep the $PetCO_2$ at the same level. The change in minute ventilation had no significant effect on cerebral oxygenation. From this we may conclude that changes in cerebral oxygenation observed during hypo- and hypercapnia are not caused by the accompanying change in minute ventilation.

Table 4 Concentration changes of oxyhemoglobin, deoxyhemoglobin, and total hemoglobin as a result of hypercapnia and hypocapnia for all age groups. The change in CBF compared with normocapnia is also given.

		Change μM/kPa		
		Age group 1 ($n=9$)	Age group 2 ($n=9$)	Age group 3 ($n=10$)
hc	O_2Hb	6.2±2.2	4.5±2.5	3.8±1.8
	HHb	−3.4±1.3	−4.1±2.1	−3.0±1.4
	tHb	2.8±1.4	0.4±1.1	0.8±0.8
	ΔCBF_{hc}	1.3±0.2	1.6±0.4	2.4±1.7
hv	O_2Hb	−1.7±1.7	−1.2±0.6	−3.1±2.4
	HHb	0.8±1.3	0.7±0.4	1.1±1.3
	tHb	−0.9±1.1	−0.6±0.5	−2.1±1.7
	ΔCBF_{hv}	0.9±0.1	0.9±0.0	0.9±0.1

4.2 AGE DEPENDENCY OF CEREBROVASCULAR CO_2 REACTIVITY

4.2.1 Hypercapnia

The ventilatory response to hypercapnia showed a significant increase for all age groups. Compared with groups 1 and 2, the ventilatory response was significantly smaller in age group 3. These data support the findings of previous studies in both men[32] and rats.[33] The reduction in minute ventilation is assumed to be related to a large reduction in mean inspiratory airflow, probably caused by a reduction in neuromuscular inspiratory output.[32]

Several investigators have examined cerebrovascular CO_2 reactivity to hypercapnia. Most of these studies discussed the possible effects of age on CO_2 reactivity, using indirect methods. The change in CBF was used as a measure for the CO_2 reactivity. Scheinberg,[21] Schieve and Wilson,[18] and Yamamoto et al.[20] found that normal aging could be associated with a reduction of CO_2 vasodilator responsiveness during hypercapnia. A normal CO_2 reactivity during hypercapnia was reported by Lassen, Munck and Tottery.[14] With NIRS it possible to look at vasodilatation of the smaller vessels directly, by monitoring the increase or decrease in tHb and the overall cerebral oxygenation. In this study we found a significantly increased change in tHb as a reaction to hypercapnia in the oldest age group. This may be caused by structural changes in the cerebral vessels which manifest with advancing age. A loss of elasticity of the cerebral vessels, causing an increase in CVR, might be one the most important changes.[18,34,35] A significant increase in CO_2 reactivity with age was found if the change in CBF during hypercapnia was used as a measure for the CO_2 reactivity. These findings do not correspond with the studies in which a normal or decreased CO_2 reactivity was found. A possible explanation for the results of this study is that the increased cerebrovascular response to hypercapnia with age occurs to compensate for the decreased ventilatory response. This is supported by the study by Peterson et al.[32] Another explanation might be a decreased autoregulatory function: a cerebral vasoconstriction to compensate for the increase in perfusion pressure with advancing age.

4.2.2 Hypocapnic Hyperventilation

CO_2 reactivity to hypocapnia with advancing age has been studied by various other researchers. Gotoh, Meyer, and Takagi[17] found a significant difference in cerebrovascular reactivity with age, the older age group showing less reaction. Their method was based on measuring arterial and (jugular) venous gases and electrolytes while recording EEG during severe hyperventilation. The study by Yamaguchi et al.,[19] using the ^{133}Xe inhalation method, showed a decreased vasoconstrictive response during hypocapnic hyperventilation with advancing age. In our study, a significant decrease in tHb during hypocapnia was found. An age effect was demonstrated: compared with age group 2, it was found that the oldest age group (age group 3) had a significantly lower tHb, and compared with the youngest age group (age group 1) it was lower but not significantly so. The overall effect, however, is small. This might be caused by methodological differences; e.g., the use of a direct versus indirect method for assessing cerebral oxygenation and interindividual variability. The results of this study assume that there are no critical changes in the capacity of the pial vessels to constrict. The significantly greater decrease in tHb, together with a (not significant) greater decrease of CBF in the elderly could be explained by the hypothesis that the increase in vasoconstrictive response is compensating for a possible failing of the ventilatory response to hypocapnia.

In Figure 2 the relationship between the individual changes in CBF, compared with normoxia, as a function of $PaCO_2$ is given for all subjects. The relationship is in good agreement with the results found in other studies on man,[36,37] dogs,[38] and monkeys.[39]

4.2.3. Cerebral Blood Volume

The mean CBV was 2.14 ml/100 g for the young subjects, 1.92 ml/100 g for the middle-aged subjects, and 1.47 ml/100 g for the elderly subjects. These values for CBV are in good agreement with other studies using NIRS,[8,12] but lower than the values reported with other methods. Toyama et al.[40] found a regional CBV of 4.0 ± 0.4 ml/100 g in 9 subjects aged 43 to 70 years. The method made use of ^{99m}Tc red blood cells and single positron emission computed tomography (SPECT). Leenders et al.,[41] using ^{15}O steady-state inhalation combined with PET, found a CBV in the gray matter of the frontal cortex of 4.3 ± 0.8 ml/100 g in 32 subjects aged 22 to 82 years. These differences can be partly explained as a consequence of the method followed. With NIRS it is not possible to monitor deep within the adult brain because of the size and the thickness of the skull. This will result in CBV values to which the relatively bloodless skin and skull might contribute significantly and therefore to an underestimation of the CBV. Furthermore, it is not completely clear which vascular compartments (besides the capillary network) contribute to the NIRS signals.

The average CBV of age group 3 was significantly lower than that for groups 1 and 2. When looking at the individual values, we found two outliers, aged 73 and 75 years, in the elderly subjects; these had strikingly high CBV values compared with the other subjects of this age group. From the anthropological literature it is known that there is a large spread in biological age around the calendar age in elderly people.[42] On the basis of their exercise activ-

ity (more then 14 hours/week) as well as ECG at rest, it can be concluded that these two subjects were biologically younger than the other subjects of the group. When the data analysis was performed again without the two outliers, the decrease in CBV in the elderly subjects becomes significantly greater ($p<0.0006$). This decrease in CBV may be due to neuronal loss and cell shrinkage with age, a mechanism also reported by others.[43,44]

The scatter diagram of CBV as a function of age for all individuals also shows a significant decrease in CBV with advancing age. Because of the two outliers, a Spearman rank correlation was used to analyze the data. Leenders et al.[41] found a greater decrease in CBV, 0.044 ml/100 g/year, a difference that is most likely due to methodological differences. Yamaguchi et al.[19] found no significant decrease in CBV with advancing age. The subjects of this study were, however, no older than 62 years which equals age groups 1 and 2 of this study.

4.3 METHODOLOGICAL CONSIDERATIONS

NIR light travels via the skull and skin into the outer layers of the cerebral tissue. Recently there has been discussion about the contribution of extracerebral contamination of the NIRS signal. In patients undergoing carotid endarterectomy, it was found that, by first clamping the external carotid artery and after 2 min the internal carotid artery, half of the patients showed changes in the NIRS signals that were not related to changes in intracranial variables. Some patients showed a biphasic response.[45] This implies that, at least in this group of patients and under anesthesia, the extracranial circulation makes a significant contribution to the NIRS signals. This, however, does not provide us with information on the contribution of the extracerebral circulation to NIRS signals during hyper- or hypocapnia. With a laser Doppler flow probe attached between the two NIRS optodes, Smielweski et al.[9] found in some cases fluctuations during hyperventilation in healthy subjects. However, these fluctuations were not correlated with either $PetCO_2$ or with the changes in the NIRS signals during CO_2 challenge.

There are two ways of minimizing the influence of the extracranial contribution to the NIRS signal. First, a large enough optode distance should be used. Germon et al.[46,47] and Harris and Bailey[10] showed that when the distance between optodes is too small, the influence of the extracranial circulation cannot be neglected. Furthermore, Germon et al. showed that the optimal optode distance will likely be between 4.5 and 5.5 cm. This is also the finding of Kirkpatrick et al.,[45] who are convinced that a minimum distance of 5 cm should be used. In our study, a distance of 5.5 cm was used in all cases, thereby ensuring a maximum contribution of the intracerebral oxygenation changes to the NIRS signal. Second, the contribution of the scalp can be minimized by applying pressure to it.[47] In this study the pressure was not applied by a tourniquet, but by the optode holder itself, which was tightly fixed around the head, with maximum pressure underneath the holder. Although the pressure itself could not be measured, we are convinced that this setup, together with a 5.5-cm optode distance, minimizes the extracranial contribution to the NIRS signal.

5 SUMMARY

The question of a physiologic, age-related change of cerebrovascular CO_2 reactivity has been raised before, but is not yet clarified. In this study a contribution toward a solution of this problem is made by using NIRS, a noninvasive method. This investigation studied the age dependency of several variables studied. An age-dependent path-length factor was used for all calculations. Phase-resolved spectroscopy was used to show that the path-length factor is age dependent: the older the subject, the longer the path length.[23] The age relationship of the path-length factor was measured in the age range of 0 to 50 years. For an age of 20 up to an age of 50, the path-length factor changes from 5.76 to 6.61 (at 807 nm). For subjects aged 51 and over, the same path length was used as for subjects aged 50. However, extrapolation to an age of 80 would give a path-length factor of 7.34. If the extrapolation is valid, this means that differences (in, e.g., CBV) between the young and old subjects become more significant than they are now considered. Ideally however, the path-length should be measured separately in each subject at the time of the study.

The calculation of the change in CBF depends on the cerebral venous oxygen concentration; we used a value of 65% in resting conditions. This value will vary among subjects and therefore will introduce an error in the calculation. Still we believe that, in a group of healthy volunteers, this method provides a good indication of the changes in CBF due to hyper- or hypocapnia. The method in which a bolus of pure oxygen, given after a slight arterial desaturation (CBV calculation), acts as a tracer to determine absolute CBF was not used for two reasons. First, the method depends on a good beat-to-beat pulse oximetry signal, which is very difficult to obtain. Second, and most important, a slight desaturation is needed to determine CBF. During the stage of the experiment where a steady state during hypo- or hypercapnia is reached, it is not possible to let this be followed by a desaturation and subsequent O_2 bolus to assess CBF.

In the oldest age group, the change in CBF found during hypercapnia was probably too high. This was caused by three outliers in the group, who showed a substantial change in CBF with only a small rise in $PaCO_2$. The change, expressed per kilopascal, then becomes very high. There are several explanations for this. An underestimation of the

$PaCO_2$ due to a temporal delay in the peripheral circulation would result in a too high change in CBF. We did check the $PetCO_2$ and found considerable discrepancy with the $PaCO_2$ that corresponded to the same time (subject number, $\Delta PetCO_2$, and $\Delta PaCO_2$ in kPa: 1, −1.2 to −0.30; −4, 1.7 to 0.41; 5, −1.4 to 0.29). Another, less likely explanation might be that extrapolation, which is needed to express values per kilopascal change in $PaCO_2$, is not allowed. Also less likely are small measurement errors in the blood gas determination, which will have a great influence on the change of CBF per kilopascal if the rise of $PaCO_2$ is small.

In conclusion, our study shows the ability of NIRS to assess cerebral hemodynamics noninvasively. Increased ventilation did not affect cerebral oxygenation. Furthermore, it was found that hypercapnia causes an increase in CBF and hypocapnia causes a decrease in CBF. Finally, it was found that the CBV in elderly people is significantly lower than the CBV in younger people, indicating neuronal loss and cell shrinkage.

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APPENDIX

CALCULATION OF CHANGE IN CBF CAUSED BY A CHANGE IN $PaCO_2$

1. In calculating CBV, the change in concentration of HHb is plotted as a function of arterial saturation (SaO_2). The slope of this relationship gives the change in concentration of HHb in micromolar per percent change in SaO_2.

2. During hyper- or hypocapnia, CO_2 tension is raised or lowered by approximately 1 kPa. The change in HHb is determined during the steady-state period and expressed in micromolar per kilopascal of change in CO_2 tension.

3. The change in HHb is compared with the slope (used for the calculation of CBV) found in step 1 and converted into an accompanying change in SaO_2.

4. To quantify the change in CBF as a function of change in arterial CO_2 tension, the following assumptions are made:

- The oxygen consumption of the brain does not change during hyper- or hypocapnia.
- For healthy subjects at rest, the jugular venous oxygen saturation is 65%.
- The plasma oxygen content is neglected.
- Vasodilatory or vasoconstrictive effects are limited to the relatively large vessels, which have little influence on NIRS signals.

5. According to the Fick principle, the oxygen uptake of the brain per unit time (Qt) is proportional to the product of CBF and arterial oxygen concentration (SaO_2) minus venous oxygen concentration ($SjvO_2$):

$$Qt \equiv CBF(SaO_2 - SjvO_2).$$

During normocapnia (nc) we get:

$$Qt_{nc} \equiv CBF_{nc}(SaO_{2_{nc}} - 65\%).$$

During hyper- or hypocapnia (hc and hv, respectively) the CBF will increase or decrease, resulting in an increase or decrease of the venous oxygen concentration ($\Delta SjvO_2$):

$$Qt_{hc,hv} \equiv CBF_{hc,hv}(SaO_{2_{hc,hv}} - 65\% - \Delta SjvO_2).$$

6. Under the assumption that $Qt_{nc} = Qt_{hc,hv}$, we find for the change in CBF during hyper- or hypocapnia:

$$CBF_{hc,hv} = CBF_{nc} \times \frac{SaO_{2_{nc}} - 65\%}{SaO_{2_{hc,hv}} - 65\% - \Delta SjvO_2}.$$

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