Systemic and cerebral hemodynamics in response to cardiovascular challenges : the heart-brain connection

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CHAPTER 4

Assessment of middle cerebral artery diameter during hypocapnia and hypercapnia in humans using ultra high-field MRI

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ABSTRACT

In the evaluation of cerebrovascular CO_2 reactivity measurements, it is often assumed that the diameter of the large intracranial arteries insonated by Transcranial Doppler (TCD) remains unaffected by changes in arterial CO_2 partial pressure. However, the strong cerebral vasodilatory capacity of CO_2 challenges this assumption, suggesting that there should be some changes in diameter, even if very small. Data from previous studies on effects of CO_2 on cerebral artery diameter (MCA) have been inconsistent.

In this study, we examined ten healthy subjects (5 female, 5 male, age 21–30 years). High resolution (0.2 mm in-plane) MRI scans at 7 Tesla were used for direct observation of the MCA diameter during hypocapnia: -1 kPa (-7.5 mmHg), normocapnia: 0 kPa (0 mmHg) and two levels of hypercapnia: +1 and +2 kPa (7.5 and 15 mmHg) with respect to baseline. The vessel lumen was manually delineated by two independent observers.

The results showed that the MCA diameter increased by 6.8±2.9% in response to 2 kPa $PetCO_2$ above baseline. However, no significant changes in diameter were observed at the -1kPa (-1.2±2.4%), and +1kPa (+1.4±3.2%) levels relative to normocapnia. The non-linear response of the MCA diameter to CO_2 was fitted as a continuous calibration curve. Cerebral blood flow-changes measured by TCD could be corrected by this calibration curve using concomitant $PetCO_2$ measurements. In conclusion, the MCA diameter remains constant during small deviations of the end-tidal CO_2 pressures from normocapnia, but increases at higher $PetCO_2$ values.

Keywords

Transcranial Doppler; MRI; Hypocapnia; Hypercapnia; Angiography; Cerebral blood flow measurement.

INTRODUCTION

Over the past three decades, Transcranial Doppler (TCD) has been extensively used in clinical and research settings for non-invasive assessment of the vasodilatory capacity of the cerebral vasculature [1]. The cerebrovascular reactivity, defined as the change in cerebral blood flow (CBF) in response to a carbon dioxide (CO_2) challenge [2], represents the vasodilatory capacity of the cerebral vasculature to changes in arterial CO_2 partial pressure. It is often assumed that the diameter of the large insonated intracranial arteries remains unaffected by changes in arterial CO_2 partial pressure [3]. Based on this assumption, changes in blood flow velocity measured with TCD in response to a CO_2 challenge are considered directly proportional to the change in CBF. However, due to the quadratic dependency of the vessel cross-section area on the diameter, even small changes in diameter would translate to considerable errors in the measurement of CBF changes by TCD. Therefore the validity of this assumption is extremely important.

To test this fundamental assumption, various techniques have been employed to assess the effect of substances, such as CO_2 and acetazolamide, which are known to change the CBF, on the diameter of the middle cerebral artery (MCA). Angiographic studies [4-6] and intraoperative measurements [7] of the MCA demonstrated that arteries smaller than the MCA, but not the MCA itself, exhibit vasodilation in response to increases in arterial partial pressures of CO_2. In contrast, comparisons of the blood flow velocity in the MCA with SPECT CBF measurements [8] or venous outflow [9] indicated an increase in MCA diameter during administration of CO_2. However, these methods are indirect measures of the MCA diameter and it is unclear whether the data reflect true changes in diameter. Direct observations using MRI-based measurements in conscious humans did not show changes in MCA diameter during hypocapnia [3,10] nor during hypercapnia [3]. In addition, results from studies with the carbonic anhydrase inhibitor acetazolamide were also contradictory. Administration of acetazolamide leads to a decreased pulmonary removal of CO_2 from the blood leading to lower blood pH. One MRI study did not detect an increase in MCA diameter following acetazolamide administration [11], while a more recent study did report an increase in MCA diameter [12]. In summary, the results from the literature on the effects of arterial CO_2 partial pressure on MCA diameter are inconsistent.

One explanation for the contradictory findings might be the limited spatial resolution of the techniques used in the aforementioned studies in terms of detecting small changes in the MCA diameter. Another explanation might be the narrow CO_2 range used.

The purpose of the present study was to measure the MCA diameter for a wide range of end-tidal CO_2 pressures with high resolution MRI at 7 Tesla and, if changes are present, to use these data to construct a calibration curve for TCD-based blood flow velocity measurements.

METHODS

Subjects

Ten healthy subjects (5 female, 5 male), aged 21–30 years, were scanned and written informed consent was obtained. Subjects refrained from drinking caffeinated beverages and eating for at least two hours prior to the experiment. The protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center.

Measurements

A gas mixture containing 21% oxygen, 79–71% nitrogen and 0-8% CO_2 was administered to the subject through a silicone face mask. End-tidal CO_2 pressure ($PetCO_2$) was measured through a cannula attached to the mask and connected to a capnograph (Capnomac Ultima, Datex, Helsinki, Finland) located outside the MRI scanner room. Heart rate and oxygen saturation were continuously monitored and blood pressure measurements were taken every 2–4 minutes using an inflatable arm-cuff (Magnitude, In-Vivo, Orlando, Florida, USA).

Protocol

Baseline $PetCO_2$ was measured during 5 minutes of rest inside the MRI scanner. Subsequently, four levels of $PetCO_2$ were applied in random order. $PetCO_2$ was varied by inhalation of CO_2 and/or hyperventilation. The target $PetCO_2$ levels consisted of -1 kPa (-7.5 mmHg), 0 kPa (0 mmHg), +1 kPa and +2 kPa (+7.5 and +15 mmHg) relative to the subject's baseline $PetCO_2$. The $PetCO_2$ was kept constant during the high resolution scans by manually adjusting the CO_2 concentration of the inspired air [13]. The desired level of $PetCO_2$ was established for at least 30 seconds prior to the scan to ensure that a steady state level had been reached before the start of acquisition. Subjects were asked to breathe deeply and keep a constant breathing frequency aided by visual and auditory stimuli inside the scanner.

MRI acquisition

All experiments were performed on a 7 Tesla whole body Philips Achieva MRI system (Philips Healthcare, Best, The Netherlands). The MCA was identified on orthogonally reconstructed axial 3D T_1-weighted scans. The parameters for the 3D T_1-weighted were: repetition time / echo time = 4.1 / 1.84 ms, flip angle = 7°, field-of-view = 246 x 246 x 174 mm^3, voxel size = 1 x 1 x 1 mm^3, scan duration 2 min. The high resolution 2D-scan was planned perpendicular to the MCA and had the following parameters: black blood T_2-weighted Turbo Spin Echo (TSE), repetition time / echo time = 2000/116 ms, refocusing angle = 110°, field-of-view = 240 x 180 x 5 mm^3, acquisition matrix = 1200 x 900, voxel size = 0.2 x 0.2 x 5 mm^3, TSE factor = 12 with additional 4 startup echoes, dynamics = 2, total scan duration = 5 min.

Data analysis

Two independent observers (JV & AGTB), blinded to subject and $PetCO_2$ level, manually delineated the MCA lumen on the high resolution MRI scan. Within- and between observer agreement was

assessed by the Intraclass Correlation Coefficient (ICC2,1, SPSS v20, SPSS Inc., Chicago, Illinois, USA). The average value of all observations per vessel was used in subsequent analysis. Data analysis was performed offline using MATLAB (vR2012a, Mathworks, Natick, Massachusetts, USA). The absolute translation and rotation with respect to the first scan of each subject were assessed using the FSL FLIRT routine (v5.0, fMRIB, Oxford, United Kingdom) with three degrees of freedom.

For each subject the MCA diameter (D) was determined from the lumen area (A), using: $D = \sqrt{4A/\pi}$. Additionally, the lumen area was expressed relative to the lumen area during normocapnia using: $A_{normalized} = A/A_{normocapnia} \cdot 100$ %, with $A_{normocapnia}$ the lumen area during normocapnia. The $\Delta PetCO_2$ was defined for each subject as the absolute difference with respect to normocapnia.

The effect of $PetCO_2$ level on vessel diameter was assessed using a mixed-effects model with post-hoc comparisons (SPSS v20, SPSS Inc., Chicago, Illinois, USA). All multiple comparisons were Bonferroni-corrected and a p-value less than 0.05 was considered significant.

The normalized vessel area was fitted using a third order polynomial curve and compared to a linear model. Goodness-of-fit was assessed with the R-square (R^2) statistic adjusted for the number of degrees-of-freedom.

RESULTS

All ten subjects successfully completed the entire protocol and a total of 40 scans were acquired. Three subjects reported slight discomfort at +2 kPa, upon which the highest $PetCO_2$ level was lowered. In one of these subjects the $PetCO_2$ had to be lowered to values which were not appropriate to the study, and this scan was excluded from analysis. One further scan was excluded by both observers because of severe motion artefacts at the highest $PetCO_2$ level. The remaining 38 scans were included in the full analysis.

The effects of $PetCO_2$ on MCA diameter, heart rate and mean arterial pressure are given in Table 4.1. Four distinct levels of $PetCO_2$ were achieved ($p<0.01$) with a minor increase in $PetCO_2$ during normocapnia compared to baseline (0.17 kPa; $p = 0.014$). Varying the $PetCO_2$ did not affect heart rate ($p = 0.187$) or mean arterial pressure ($p = 0.078$). The image quality was sufficient to be able to visualize and outline the vessel lumen for all $PetCO_2$ conditions (Figure 4.1). The absolute displacements of the head relative to the first scan were 1.6 mm and 2.3 mm in the x and y directions, respectively, with a small in-plane rotation of 0.7°. Within-observer agreement was very high for both observers, ICC = 0.94 and 0.97 for JV and AGTB respectively. Measurements were also consistent between observers, ICC = 0.86, albeit with a significant mean difference of 0.16 mm ($p<0.001$, paired *t*-test).

Table 4.1 | Effects of $PetCO_2$ on hemodynamic variables and middle cerebral artery diameter.

	Diameter (mm)	$PetCO_2$ (kPa)	HR (bpm)	MAP (mmHg)
Baseline		4.9±0.5	67.5±11.7	81.7±4.7
Hypocapnia	3.19±0.27	3.8±0.5†	69.0±12.9	83.9±7.0
Normocapnia	3.23±0.26	5.1±0.5†	67.1±12.4	83.4±7.0
Mild hypercapnia	3.28±0.33	6.0±0.5†	67.3±12.5	84.1±6.2
Moderate hypercapnia (N=8)	3.42±0.33*	6.8±0.6†	70.2±12.3	88.0±6.3

Data (N=10) are represented as mean ± SD. *p<0.001 vs hypo- (-1 kPa), normo- (+0 kPa), and hypercapnia (-1 kPa). †p<0.001 vs baseline condition. (Bonferroni-corrected)

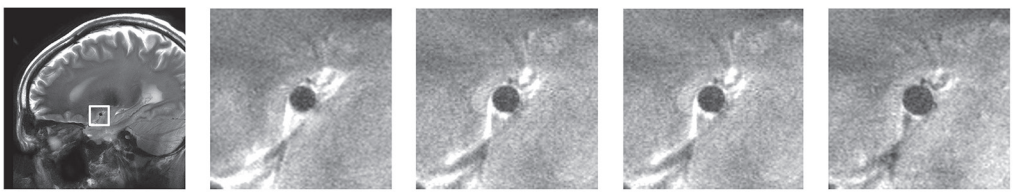

Figure 4.1 | Representative example of high resolution MRI scans planned perpendicular to the MCA. From left to right: the white square depects the location of the zoomed images; zoomed image at hypocapnia (-1 kPa), baseline normocapnia (0 kPa), and hypercapnia (+1 and +2 kPa end-tidal CO_2) respectively.

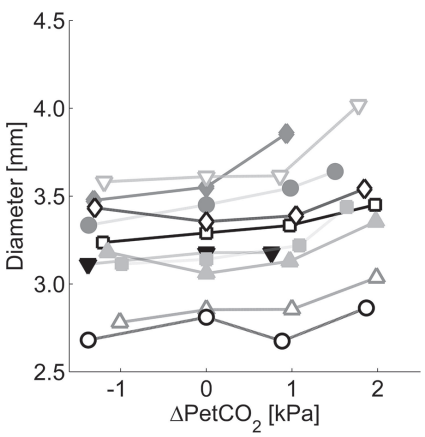

Figure 4.2 | Effect of $\Delta PetCO_2$ (kPa) on absolute middle cerebral artery diameter (MCA). The $\Delta PetCO_2$ is relative to the subject's resting baseline in the scanner. Variation in MCA diameter can be observed between subjects. Different subjects are indicated with distinct symbol and color.

There was a significant effect of $PetCO_2$ level on MCA diameter ($p<0.001$, Figure 4.2) with a 6.8±2.9% increase in vessel diameter at +2 kPa hypercapnia. No significant differences were observed at -1 kPa hypocapnia (-1.2±2.4%), or +1 kPa hypercapnia (+1.4±3.2%) compared to normocapnia. The effect of $\Delta PetCO_2$ on normalized vessel area is depicted in Figure 4.3. The normalized lumen areas for the -1, +1 and +2 kPa $PetCO_2$ levels relative to normocapnia were 98±5%, 103±6% and 114±6%, respectively. A non-linear $PetCO_2$ – MCA cross-sectional area relationship was established using a third-order model (R^2_{adj} of 0.51 versus a R^2_{adj} of 0.44 for a linear relation) with the normalized MCA area (*y*) approximated by: $y = 0.93x^3 + 1.22x^2 + 1.99x + 99.64$, where *x* denotes $\Delta PetCO_2$ in kPa.

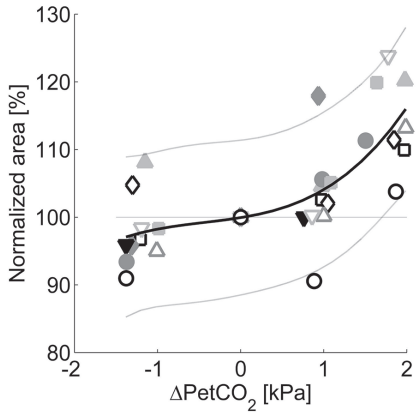

Figure 4.3 | Effect of $\Delta PetCO_2$ (kPa) on middle cerebral artery (MCA) area relative to normocapnia. The MCA area is expressed as a percentage of normocapnia and the $\Delta PetCO_2$ is relative to the subject's resting baseline in the scanner. The data is modeled with a 3rd order polynomial (thick-line) and 95% confidence interval (dotted-lines). Identical symbols as in Figure 4.2 are used.

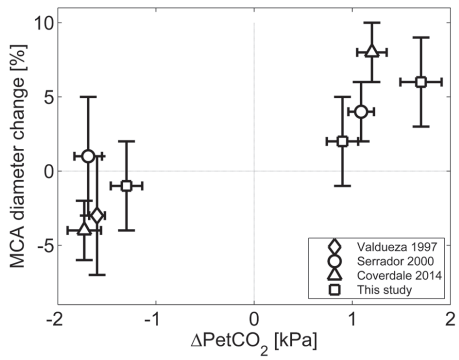

Figure 4.4 | Graphical summary of MRI studies directly observing the MCA during CO_2 challenges [3,10,17]. Data are presented as percentage change in diameter as function of $PetCO_2$ (mean+/-SEM). Data from Serrador et al. [3] are derived from their Figure 4.3. All studies employed $PetCO_2$ measurements with exception of Valdueza eta al. [10] that used $PaCO_2$. $PaCO_2$ is comparable to $PetCO_2$ during hypocapnia [23].

DISCUSSION

The major finding of the present study is the non-linear behavior of the MCA in response to hypercapnia with (proximal) vasodilatation at a $PetCO_2$ level of +2 kPa above normocapnia, and constancy of the MCA diameter in the lower $PetCO_2$ range (-1 to +1 kPa). The clinical implication is that the often-assumed constant value of the MCA diameter linking TCD blood flow velocity measurements to CBF is not valid for $PetCO_2$ levels between +1 and +2 kPa, leading to underestimation of the underlying CBF response.

The present data complements those from Serrador et al. [3] by extending the $PetCO_2$ range to +2 kPa hypercapnia. Data from the present study confirm their earlier observations that the MCA diameter does not change in the lower $PetCO_2$ range up to 1 kPa above baseline. This result has also been confirmed using a variety of methodologies, including angiography [4,6,5], surgical microscopy [7], TCD [9,14-16] and MRI [3,10]. A recent MRI study by Coverdale et al. [17], investigated the MCA diameter response to 6% CO_2 inhalation. Whereas the present study detected a significant difference in MCA diameter of 6.8% at the highest $PetCO_2$ level (+2kPa), they observed an 8% increase at a lower $PetCO_2$ of +1.2 kPa. Moreover, they indicated a significant decrease in diameter of -4% during hypocapnia (-1.7 kPa), whereas the present study observed a non-significant decrease of -1.2% at a slightly milder hypocapnia level of -1.3 kPa. To reduce the subject dependent reaction to a fixed CO_2 step (e.g. inhalation of 6% CO_2), the present study employed controlled $PetCO_2$ levels relative to the baseline of each subject. Together with a higher resolution and larger observed mean diameter in the present study this might explain the differences in the observed MCA diameter changes between the two studies. Both studies used similar subject population and MRI acquisition technique, suggesting strongly that the MCA diameter is responsive to $PetCO_2$ levels above +1 kPa. This is in line with a previous observation in the +2 kPa $PetCO_2$ range using color Doppler [18], which found an increase in the carotid artery diameter, in turn suggesting that the vasoactive effects of P_aCO_2 are not limited to the smaller cerebral arteries [4-7].

In order to place the MCA diameter changes observed in the present study into context, the results from the present study and previous literature are graphically depicted in Figure 4.4. Data are taken from those studies that directly observed the MCA using MRI [3,10,17]. During hypercapnia all studies observed an increased diameter, although this was not statistically significant in all studies. During hypocapnia the observations are more variable, suggesting that the diameter changes, if present, might be small compared to changes observed during hypercapnia. Based on physiological principles, it might be expected that the MCA diameter – $PetCO_2$ relation would be sigmoidal [19]. However, an upper and lower bound to the MCA diameter changes are not established by the current data.

The cerebrovascular reactivity is defined as the increase in CBF per unit CO_2 [2]. Inhalation of 5–6% CO_2 is a common method to quantify the cerebrovascular reactivity, and increases the $PetCO_2$

by 1 to 2 kPa [8,20], with a 3.8%/mmHg increase in CBF in healthy subjects [19]. This implies a CBF increase of 57% at +2 kPa, which should be compared to an underestimation of 14% of the CBF-change by TCD due to the increase in MCA diameter (6.8%). The accuracy of such TCD measurements is diminished if this bias is not accounted for. Clinical guidelines currently do not correct for diameter changes at higher levels of $PetCO_2$ and the new data on the $PetCO_2$ – MCA diameter relation may be of particular importance for cerebrovascular reactivity measurements in a multi-modal setting.

Among the strengths of the present study is the relatively high in-plane resolution of 0.2 mm that enabled the detection of a mean increase in MCA diameter of 6.8%. The physical resolution of previous studies ranges from 0.27 mm [11] to up 0.7 mm [4,10], which, based on our diameter measurements, corresponds to a detection limit of 8.5%–22%. The sensitivity and limited range of $PetCO_2$ levels in previous studies may have prevented the detection of small changes in diameter. In the present study no changes in MCA diameter between -1 to +1 kPa $PetCO_2$ compared to baseline levels were identified. This may well be in agreement with other studies, but we cannot exclude that conclusion that the absence of an observed diameter change in the lower $PetCO_2$ ranges could still be related to technical limitations, such as the spatial resolution of 0.2 mm.

The calibration curve, as presented in Figure 4.3, can directly be related to an over- or underestimation of the CBF-change measured by TCD. For practical purposes the non-linear relationship between arterial cross-sectional area and $PetCO_2$ was approximated by a third order polynomial curve without prior physiological assumptions, enabling the possibility to correct TCD measurements by concurrent $PetCO_2$ measurements. This assumes that a smooth fit to all available data points best approximates the underlying physiological response, even though only at the highest $PetCO_2$ level was a significant difference in MCA diameter found. The variation observed between subjects in relative area changes might suggest that the sensitivity to $PetCO_2$ is subject-specific. This variation gives rise to the large confidence intervals of the calibration curve.

Whether (small) MCA diameter changes are of practical value depends on the precision of the TCD and $PetCO_2$ measurements and the change in CBF that is considered relevant in a clinical or scientific context. Continuous TCD measurements are quite stable during rest, provided that the probe is adequately fixed to the head. The uncertainty (standard error of the mean) of TCD flow velocity measurements during 3 consecutive 1-minute recordings is, on average, 1% [10 subjects, unpublished data]. An underestimate of 1% in the CBF determination, due to the concomitant increase in MCA diameter, corresponds to the $\Delta PetCO_2$ being higher than +0.4 kPa according to the calibration curve. This value should be compared to the typical precision of $PetCO_2$ measurements of 0.24 kPa [present study, unpublished data]. At a $\Delta PetCO_2$ of +0.4 kPa and a precision of 0.48 kPa (2 times standard deviation) the calibration curve gives a 1% uncertainty in the vessel cross-sectional area. Therefore, without more precise $PetCO_2$ measurements area, changes smaller than 1% do not improve the accuracy of CBF-changes measured by TCD. However, an underestimation of 1% is one order magnitude smaller than the flow-changes expected in clinical practice.

Several limitations exist in this study. First, the sensitivity of the MRI contrast to in- or outflow of blood might affect the apparent diameter of the MCA. In the current study black-blood imaging was used, which is inherently dependent on the outflow of blood and gives a complete signal void in the vessel lumen when the blood flow velocity is sufficiently high [21]. The use of four startup echoes and long echo time further reduces the value of the minimum blood flow velocity for which a signal void occurs. Additionally, the observed contrast of the vessel lumen in the present study is consistent for all $PetCO_2$ levels. Therefore, it can be assumed that the effect of blood flow on the diameter measurements was negligible. It should be noted that some earlier studies [10-12]used time-of-flight (TOF) imaging to assess the vessel diameter. In TOF imaging the brightness and extent of the vessel depends on the inflow of blood [22]. Hence, the apparent diameter of the vessel is influenced by the blood flow through the vessel, which is strongly dependent on the $PetCO_2$ level. Therefore, black-blood imaging, as used in the current study, should be considered more suitable to measure vessel diameter during $PetCO_2$ variation.

During normocapnia and hypercapnia a difference exists between the measured $PetCO_2$ and the arterial CO_2 partial pressure ($PaCO_2$) [23], which could have introduced some variation in the MCA diameter measurements. In a fixed body position, the $PetCO_2$ – $PaCO_2$ relation is linear [23-25] . In the present study the subjects remained in the supine position and breathing rate and depth was controlled by visual and auditory stimuli. Therefore, a linear relation between $PaCO_2$ and $PetCO_2$ was assumed. Little or no influence of the $PaCO_2$ – $PetCO_2$ difference is expected on the variability of the MCA diameter measurements. In most applications $PetCO_2$ is readily available, making it a more suitable parameter for accounting for the effect of CO_2 on flow-change measurements by TCD.

Subject head-motion between individual scans could introduce errors in the lumen area measurements. This motion would lead to a non-perpendicular intersection of the imaging slice with the MCA, leading to an overestimation of the lumen area. This study used a 2D-scan planned perpendicular to the MCA. Therefore it was not possible to assess the head motion for any out-of-plane translations and rotations. To estimate the potential impact of such motions, the extent of in-plane motion was used as a proxy for the out-of-plane translation and rotations. Limited in-plane translation and rotation was observed. Therefore, by extension, overall head motion and out-of-plane movement between scans was deemed to be small. Moreover, the image quality was consistent between dynamics and only one out of total 40 scans was excluded due to poor image quality caused by movement artefacts. Therefore, head motion is considered only a minor concern for this study.

This study was performed in a relatively small number (N=10) of young healthy subjects. Increased age has been associated with cardiovascular degradation including atherosclerotic changes and arterial stiffening [26], which reduces the ability of the arteries to vasoconstrict and vasodilate. Therefore, the vasodilatory response of the MCA to CO_2 might be reduced in an older population compared to the young subjects measured in the present study. This might be one of the

explanations for the discrepancy between the results obtained by Schreiber [11] in a population with internal carotid stenosis with mean age of 62 years compared to the present study with a mean age of 23 years. Finally, only the MCA was considered in the present study. The protocol was limited to one artery due to constraints on the total examination time per subject. The MCA is a common target for TCD insonation as it supplies a large part of the cerebral hemisphere. It is currently unknown whether the observed diameter changes of the MCA could be extrapolated to other cerebral arteries, such as the anterior- and posterior cerebral arteries.

CONCLUSION

This study found a non-linear vasodilatory response of the middle cerebral artery diameter under hypercapnic conditions. High resolution MR imaging at 7 Tesla in combination with CO_2 inhalation was able to measure the vasodilatory effect at a $PetCO_2$ level of +2 kPa above baseline, but not during -1 kPa (hypocapnia) or +1 kPa (hypercapnia). This indicates that the blood flow velocity changes measured with TCD underestimate underlying changes in CBF under high hypercapnic conditions. The proposed calibration curve can be used to correct such underestimations of CBF changes measured by TCD.

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CHAPTER 5

Using high field magnetic resonance imaging to estimate distensibility of the middle cerebral artery

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