Middle Cerebral Artery Blood Flow Velocity Changes in Response to Precise Targeting of End-Tidal CO_2 and O_2: A Comparative Study Between Transcranial Doppler Ultrasound and Phase Contrast Magnetic Resonance Angiography

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Introduction: Measuring cerebral blood flow (CBF) change in response to a vasoactive stimulus, a parameter known as cerebrovascular reactivity (CVR), is an increasingly relevant tool for the clinical assessment of cerebrovascular disease.[1] Various imaging modalities for acquiring CBF change are available, including transcranial Doppler ultrasonography (TCD) and MRI. TCD evaluation of flow velocity in vessels is convenient as it is non-invasive, inexpensive, and readily accessible. Disadvantages of this method are operator dependence, variability, and that measurements can only be performed through small acoustic windows of the head thus limiting TCD assessment to the major arteries within the circle of Willis at constrained angles.[2,3] Phase contrast MR angiography (PCMRA) provides an attractive alternative for blood flow velocity quantification as it is also non-invasive and can achieve double-oblique measurements throughout the entire brain. Previous attempts to correlate TCD and PCMRA readings in the brain, with and without a stimulus, have produced inconsistent results.[4,5] However, all of these studies suffer from a lack of control of the subjects' arterial CO_2 and O_2 levels, which have a direct affect on CBF. We therefore propose to utilize a reproducible CO_2 stimulus with precise end-tidal PCO_2 ($P_{ET}CO2$) and PO_2 ($P_{ET}O_2$) targeting to compare blood flow velocities changes in the middle cerebral artery (MCA) using both TCD and PCMRA.

Methods: Four healthy male volunteers (21 to 31 years) were recruited to measure blood flow velocity in their left and right MCA during baseline and hypercapnia using TCD as well as MRI. Reproducible delivery of a CO_2 stimulus was achieved using a computer controlled gas sequencer (RespirAct™, Thornhill Research Inc., Toronto, Canada)[6], which maintains precise $P_{ET}CO_2$ and $P_{ET}O_2$ levels in close agreement with arterial blood gas values.[7] In our study, subject $P_{ET}O_2$ values were clamped at 100 mmHg and $P_{ET}CO_2$ were either held at 40 mmHg (baseline) or 45 mmHg (hypercapnia) for the duration of the measurements. TCD evaluation was conducted with a 2.0 MHz ultrasound machine (iU22 xMatrix; Philips Electronics, Best, the Netherlands) operated by an experienced sonographer (A M). Subjects (in supine position) were exposed to the stimulus while the sonographer used an ultrasound probe to isolate a consistent portion of the MCA with the highest blood flow values to calculate the time-averaged peak velocity (TAPV). Upon completion of each MCA, the location of the probe was marked with a glycerol-water capsule and the insonation depth was recorded for the purpose of TCD angle correction as well as a spatial reference for MRI. Immediately following the TCD assessment, the subjects underwent a 3D time-of-flight (TOF) angiogram on a 3.0T MRI scanner (MAGNETOM Tim Trio; Siemens Medical Solutions, Erlangen, Germany) to locate the position of the capsule markers relative to the MCA. A spherical perimeter with radius corresponding to the recorded insonation depth was projected out from the capsule to identify the approximate portions of the MCA where the TCD measurements were taken. With the aid of the gas sequencer, baseline and hypercapnia PCMRA scans were then performed on the corresponding portions of the MCA for each subject. The imaging parameters for the PCMRA sequence were as follows: TR/TE = 52.75/5.17 ms, FA = 30°, matrix = 364×448, voxel size = 0.4×0.4×5 mm, bandwidth = 399 Hz/pixel, velocity encoding (V_{enc}) = 100 cm/s, acquisition time = 3.5 minutes. TAPV from the PCMRA data was calculated by translating the phase information into velocity values based on the V_{enc} (with aliasing correction), averaging each voxel over the entire cardiac cycle, and then selecting the voxel in the MCA that has the highest time-averaged velocity. Angle correction of the TCD data was performed by applying a cosine factor of the angle between the ultrasound measurement and the direction of the blood flow, which was determined by analyzing the 3D TOF MRA. Subject CVR for both modalities was then expressed as the difference between hypercapnia and baseline blood flow velocities, divided by the change in $P_{ET}CO_2$ and normalized by the baseline velocity on each side. The mean and coefficient of variation (CV) for each group of measurements were calculated and statistical paired t-test analysis was performed between TCD (with and without angle correction) and PCMRA velocities, as well as between the corresponding CVR values.

Results: End-tidal targeting of PCO_2 and PO_2 for each subject was achieved with minimal fluctuations resulting in standard error mean (SEM) of 0.14 for CO_2 and 0.31 mmHg for O_2 throughout the duration of the TCD and MRI measurements. PCMRA produced markedly lower mean velocities at baseline and hypercapnia relative to TCD values, with and without angle correction (see Table 1). TCD velocities had the highest CV (35.1% baseline, 30.4% hypercapnia), which improved after angle correction (30.3% baseline, 28.3% hypercapnia). In contrast, PCMRA data exhibited the lowest CV (20.5% baseline, 19.3% hypercapnia). Initially, the TCD values did correlate with PCMRA results ($r^2 = 0.47$, $p = 0.06$ baseline, $r^2 = 0.64$, $p = 0.02$ hypercapnia) but was adversely affected after angle correction ($r^2 = 0.09$, $p = 0.47$ baseline, $r^2 = 0.04$, $p = 0.63$ hypercapnia). The CV for CVR was much lower in PCMRA (29.7%) vs. TCD (65.3%), and the correlation between the two modalities was also very low with $r^2 = 0.11$, $p = 0.43$.

Discussion: Both imaging modalities, TCD as well as PCMRA, were able to measure the same physiological flow parameters in the MCA. TCD provided, on average, higher TAPV measurements of the MCA but also had higher variation compared to PCMRA results. Consequently, PCMRA appears to be more reliable based on the consistency of the CVR calculations. The velocity discrepancy between the two methods is probably due to the coarser spatial resolution of the MR images resulting in partial volume effects. A larger study is required for a more extensive statistical analysis.

References: 1. Mandell DM, *et al.*, Stroke, **39**:2021-8, (2008); 2. Spilt A, *et al.*, J Magn Reson Imaging, **16**:610-6, (2002); 3. Aaslid R, *et al.*, J Neurosurg, **57**:769-74, (1982); 4. Valdueza JM, *et al.*, AJNR, **18**:1929-34, (1997); 5. Seitz J, *et al.*, J Neuroimaging, **11**:121-8, (2001); 6. Slessarev M, *et al.*, J Physiol., **581**:1207-19, (2007); 7. Ito S, *et al.*, J Physiol., **586**:3675-82, (2008);

Table 1. TAPV at baseline (BL) and hypercapnia (CO2) for TCD and PCMRA of each subject. Corresponding CVR and statistical values in bold. Angle correction did not change CVR (%) value in TCD.

		TCD				**TCD (angle corrected)**			**PCMRA**		
		$TAPV_{BL}$ (cm/s)	$TAPV_{CO2}$ (cm/s)	Depth (cm)	**CVR (%)**	Angle	$TAPV_{BL}$ (cm/s)	$TAPV_{CO2}$ (cm/s)	$TAPV_{BL}$ (cm/s)	$TAPV_{CO2}$ (cm/s)	**CVR (%)**
Subject 1	R	92.8	100.0	4.7	**1.5**	29°	106.1	114.3	60.5	76.9	**5.4**
	L	87.7	104.0	5.0	**3.7**	35°	107.1	127.0	77.9	89.5	**3.0**
Subject 2	R	60.5	67.7	5.3	**2.4**	48°	90.4	101.2	49.4	58.6	**3.7**
	L	47.7	61.4	5.1	**5.7**	63°	105.1	135.2	42.4	48.6	**2.9**
Subject 3	R	45.8	48.0	5.5	**0.1**	44°	63.7	66.7	44.2	55.6	**5.2**
	L	30.4	44.2	5.7	**9.0**	40°	39.7	57.7	53.2	64.9	**4.4**
Subject 4	R	54.5	72.2	5.4	**6.5**	28°	61.7	81.8	59.8	70.6	**3.6**
	L	60.9	71.9	4.3	**3.6**	50°	94.7	111.9	61.8	68.6	**2.2**
Mean (±SEM)		**60.0±7.4**	**71.1±7.7**	**-**	**4.2±0.7**	**42°**	**83.6±9.0**	**99.5±9.5**	**56.2±4.1**	**66.7±4.6**	**3.8±0.4**
CV %		**35.1**	**30.4**	**-**	**65.3**	**-**	**30.3**	**28.3**	**20.5**	**19.3**	**29.7**