Published in final edited form as:

Ultrasound Med Biol. 2014 November ; 40(11): 2692–2699. doi:10.1016/j.ultrasmedbio.2014.05.022.

Middle cerebral artery blood flows by combining TCD velocities and MRA diameters: *in vitro* and *in vivo* validations

Yonan KA*, Greene ER*,⁺ Sharrar JM⁺, Caprihan A⁺, Qualls C⁺, and Roldan CA⁺

*Department of Biology and Chemistry and Department of Computer of Mathematical Sciences, New Mexico Highlands University, Las Vegas, New Mexico 87701

⁺Department of Internal Medicine and Cardiology Division, University of New Mexico School of Medicine, Albuquerque, New Mexico 87131

Abstract

Noninvasive transcranial Doppler (TCD) is widely used for blood velocity (BV, cm/sec) measurements in the human middle cerebral artery (MCA). MCABV measurements are accepted as linear with MCA blood flow (MCABF). Magnetic resonance angiography (MRA) provides measurements of MCA lumen diameters that can be combined with TCD MCABV to calculate MCABF (ml/min). We tested the precision and accuracy of this method against a flow phantom and *in vivo* proximal internal carotid artery blood flow (ICABF). *In vitro* precision (repeated measures) and accuracy (versus time collection) gave correlations coefficients of 0.97 and 0.98; respectfully (both $p < 0.05$). *In vivo* precision (repeated measures) and accuracy (versus ICABF) gave correlation coefficients of 0.90 (left and right), and 0.94 (left) and 0.93 (right) (all $p < 0.05$). Bilateral MCABF in 35 adults were similar (left, 168 ± 72 ml/min; right, 180 ± 69 ml/min; $p > 0.05$). Results suggest that blood velocity by TCD and lumen diameter by MRA can be combined to estimate absolute values of MCABF.

Keywords

magnetic resonance angiography; transcranial Doppler; middle cerebral artery blood flow; middle cerebral artery blood velocity; middle cerebral artery lumen diameter; internal carotid artery blood flow; flow phantom; *in vitro* and *in vivo* validation

Introduction

With its high temporal resolution, low cost, portability, robustness, and monitoring capability in moving subjects, noninvasive transcranial Doppler (TCD) is a well-established method to measure absolute values (cm/s) and percentage changes in human middle cerebral artery (MCA) blood flow *velocities* (BV) (Arnolds et al. 1986; Hatab et al. 1997; Martin et

Address of correspondence: ER Greene, Professor of Engineering and Biology, Research Professor of Engineering and Medicine, New Mexico Highlands University, POB 9000, Las Vegas, NM 87701, greene_d@nmhu.edu, Phone 505.454.3365.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

al. 1994; Muller et al. 1991; Panerai 2009; Newell et al. 2004; Purkayastha and Sorond 2013). Unlike other methods, inexpensive TCD is extensively used on subjects who cannot move (Martin et al. 1994) or indeed moving subjects (Lyngeraa et al, 2012; Hellsstrom et al, 1996). From the standard Doppler equation and the law of the conservation of mass (Gill 1985; Kremkau 1993; Nicholas et al. 1998) and if the unmeasured Doppler angle of insonation and MCA lumen diameters are assumed to be constant, percent changes in MCABV are linear with percent changes in MCA blood flow (MCABF) (Lipsitz et al. 2000; Mitsis et al. 2009; Zhang et al. 1998).

Although it does not measure absolute global, regional, or local cerebral blood flows or perfusions, MCABF supplies the majority (~80%) of human cerebral hemispheric blood flow (Moore et al, 2007). Thus, percent changes in MCABV are used widely as a physiological and clinical tool to reflect *changes* in human hemispheric cerebral *blood flow*.

Nevertheless, without an independent measurement of a time-average and assumed circular lumen diameter (LD), and thus an assumed and calculated circular cross sectional area of the MCA, absolute values of MCABF (ml/min) are unavailable (Bishop et al. 1986; Poulin et al. 1996; Serrador et al. 2000). With an independent measurement of LD, these dynamic and portable measurements of BV (cm/s) by TCD can be calibrated into MCABF (ml/min) and used to *estimate* human hemispheric blood flow (Gonzalez-Alonso et al. 2004; Soustiel et al. 2003). Clearly, extending one dimensional blood *velocity* measurements into three dimensional blood *flow* measurements has significant physiological usefulness in the determination of cellular, tissue, and organ transport phenomena.

With recently improved temporal, spatial, and dynamic resolutions, time-of-flight magnetic resonance angiography (MRA) is a relatively accurate, precise, and noninvasive method for the measurement of MCALD in stationary humans (Stock et al. 1996; Tarasow et al. 2007). Measurements of MCABV and MCABF can also be obtained with MRA, but the subject must be motionless and highly constrained in a generally non-portable, sometimes claustrophobic, and expensive magnet. Unlike highly portable and robust TCD methods that can be used in ambulatory, exercising, running, or physically working subjects, a motionless or unmovable subject seriously limits the types of interventional studies that can be performed with MR techniques or other historical, invasive methods for measuring human cerebral blood flow..

Thus, TCD can provide dynamic, inexpensive, bedside, ambulatory, outdoor, rural, and portable monitoring of MCABV, but not MCALD and thus not MCABF. Conversely, MRA can measure MCALD, MCABV, and thus MCABF, but only in highly specialized centers, in highly controlled conditions, and very limited interventions. After much discussion and debate, the temporal mean LD is generally considered not to change measurably or significantly during *most* physiological and clinical conditions and over moderate lengths of time (Schreiber et al. 2000; Valdueza et al. 1997). Thus, it generally is assumed to be constant. Consequently, a single measurement of LD could be used to calculate MCABF from MCABV throughout most physiological studies and interventions (Serrador et al. 2000).

Surprisingly, these two independent measurements, MCABV by TCD and MCALD by MRA, have not been combined to provide quantitative values of MCABF (ml/min) where:

$$MCABF = \left[(MCABV) (\pi) (MCALD)^2 \right] / 4$$

Here, we use the standard assumption that the blood velocity profile is relatively blunt across the lumen throughout the cardiac cycle (Nichols and O'Rourke 1998). Thus, the envelope of the relatively narrow band Doppler spectral waveforms represents the dynamic, spatial average velocity (Gill 1985; Kremkau 1993). As often reported, we also assume that small, cyclic changes in LD have minimal effects (<4%) on MCABF calculations (Eriksen 1992). Consequently, we assume that under most physiological conditions, the complex convolution of the integrated velocity and diameter waveforms generally is unnecessary.

If validated, TCD could then be easily calibrated with a single MRA measurement of MCALD to give dynamic measurements of MCABF (an *index* of hemispheric BF) under a wide range of clinical and physiological circumstances, conditions, and interventions. Currently, these options would be impossible with any other cerebral blood flow and perfusion techniques. As a field and bedside tool, the usefulness of the TCD could be enhanced with an independent measurement of MCALD by MRA.

We present a new method that could be used mostly as a tool for physiologists and neuroscientists who need robust, dynamic, and absolute measures of human hemispheric MCABF (ml/min). Thus, we used the strengths of both methods and combined BV by TCD and LD by MRA measurements to calculate MCABF. We tested the precision (repeated measures) and the accuracy (comparison to a standard) and of this new duplex method both *in vitro* (time collection phantom flows) and *in vivo* (well validated, proximal internal carotid artery blood flows, ICABF). Results suggest that MCABF measurements are relatively accurate and precise. Data are consistent with previously reported theoretical and experimental values. Thus, the method may be useful to *estimate* mass transport to the human cerebral hemispheres during a wide variety of conditions.

Methods

Transcranial Doppler

We used a commercially available, bilateral 2 MHz TCD (DWL, Doppler Box, Singen, Germany) to insonate the proximal M1 section of the left and right MCA by standard, well described methods (Arnolds et al. 1986; Hatab et al. 1997; Panerai 2009; Newell et al. 2004). The mechanical and thermal indices, safety exposure parameters as measured by the manufacture, were 0.465 and 1.99; respectively. After optimization (minimal Doppler angle with maximal signal to noise ratio) of the bilateral Doppler spectral waveforms to determine BV, the dual 4.0 cm diameter focused transducers were held securely in the optimal acoustic window by a firm and adjustable headband in the supine, resting subject. Figure 1 shows the orientation of the Doppler transducer and the MCA and typical Doppler spectral BV waveforms. Using the multigate M-mode display to orient the lumen wide sample volume and optimize the spectral signals within the MCA, the temporal mean of BV was calculated

both online and offline from the relatively narrow band spectral envelope of 6 consecutive waveforms by a single, blinded observer. The total TCD data acquisition time to determine a time averaged value of BV bilaterally was approximately 5-10 minutes. Transducer fixation and multigate, spatial M mode monitoring maximized the signal stability and signal to noise ratio and minimized signal artifacts.

Magnetic Resonance Angiography

We used a commercially available MRA with a 1.5 Tesla magnetic imaging scanner with an 8-channel head coil (Siemens, Sonata, Malvern, Pennsylvania). This standard clinical procedure has been well described (Krabbe-Hartkamp et al. 1998; Ozsarlak et al. 2004; Ruggieri et al. 1998). The total time of the MRA protocol, including perfusion and angiographic measurements, was approximately 1 hour and operated within FDA safety guidelines (specific absorption rate <3W/kg/10min). Figure 1 shows the orientation of the MCA with the MRA topographic planes and typical cross sectional lumen images. In the resting and supine subject, we used a standard 3D time-of-flight sequence (TR/TE = 33/17.4 ms, flip angle=25°, field of view (FOV) = 256 × 256 mm, matrix size = 192 × 256, slice thickness = 0.8 mm, gap=2.5mm). MRA images were evaluated in Osirix software, an open source DICOM viewer available on the internet. Extrapolation algorithms allow displays of useful 3D compilations from the 2D image slices (Rosset et al. 2004). This allowed for careful identification and evaluation of the MCA, away from bifurcations or imaging flaws. MCALD was evaluated as a perpendicular measurement while viewing the M1 section of the MCA lengthwise, rather than facing the lumen to avoid errors due to the perspective of the viewing angle. The average MCALD was calculated (by a blinded observer) from 4 independent caliber measurements with a phantom accuracy of approximately ±10% (as provided by manufacturer). MCALD measurement time from the images was ~ 10-15 minutes

In Vitro Validation

We used a custom built, multivessel, flow phantom that mimicked *in vivo* conditions in the MCA (Ramnarine et al.1998; Greene 2010). The urethane conduit (0.40 cm LD, 1.5mm wall thickness) contained ~5% backscattering particles (~5µm) in a fluid with similar density, viscosity, and attenuation properties to blood. *In vitro* blood velocity pulsatile waveforms, vessel wall distensibilities, complete insonation of the vessel lumen by the sample volume, vessel depths, and Doppler angles (~0 degrees) were similar to *in vivo* conditions. TCD BV and caliper measured LD were used to calculate phantom MCABF. Time collection was used as the gold standard for absolute flows (ml/min). We used 30 paired measurements of MCABF (repeated measures and time collection) over the range of 0-500 ml/min to determine *in vitro* precisions and accuracies.

In Vivo Validation

There is no current *in vivo* gold standard for accuracy for MCABF measurements. Nevertheless, we reasoned that in spite of various collateral and intermediate outflows, anatomically and physiologically, normal distal MCABF should correlate with the well accepted and standard imaged guided proximal measurements of internal carotid artery

blood flow (ICABF). We used a commercially available and FDA certified, imaging Doppler (Acuson 128, Mountain View, CA) to measure ICABF ~1cm distal to the bifurcation. Measurements of ICABF by this approach have been well validated (Scheel et al, 2000a; Schoning et al, 1996; Sousteil et al, 2003). Thus, absent a gold standard, we used proximal ICABF as the *in vivo* validation of measurements of MCABF.

After IRB approval, 35 adults (mean age 36 ± 11 , 31 female) underwent both bilateral MRA and TCD examinations (70 MCAs) to determine MCABF. Most subjects (92%) underwent both examinations within 72 hours (maximum of 144 hours). A subset of 16 subjects with < 2 hours between MCABF and ICABF measurements were used in their comparison. To determine *in vivo* precision duplicate and consecutive (<30 minutes with new transducer fixation, sample volume location, and MCA orientation) MCABF measurements were made in all 16 adults (8 left and 8 right). All measurements were made in the resting, supine position during normal respiration (~10-12 cycles/min). As respiration was relatively unchanged, PCO₂ was unmeasured and assumed to be constant.

Statistics

Means and standard deviations of the measurements of bilateral MCABV and MCALD and calculations of MCABF were determined (n=70). We used standard paired t tests to determine left and right side MCABF differences. Standard Pearson correlations were used to determine *in vitro* and *in vivo* precisions and accuracies. Slopes were compared to identity (1.0). A p<0.05 was considered significant.

Results

Technically adequate signals were obtained in all subjects. Individual bilateral MCABV by TCD, MCALD by MRA, and MCABF calculation in 35 adults are shown in Figure 2. Although with large variances, bilateral MCABF in 35 adults were similar with no significant differences (left, 168 ± 72 ml/min; right, 180 ± 69 ml/min). Values are consistent with limited published theoretical and experimental data. In the 16 adults (Figure 3) both MCABF and ICABF correlated bilaterally ($r = 0.76$, $r = 0.71$, $p < 0.05$; respectively). *In vitro* precision (repeated measures) and accuracy (versus time collection) gave correlation coefficients of 0.97 and 0.98; respectively (both $p < 0.05$) (Figures 4 and 5). *In vivo* precision (repeated measures) and accuracy (versus ICABF) gave correlation coefficients of 0.90 (left and right combined) and 0.94 (left) and 0.93 (right); respectively (all $p < 0.05$) (Figures 6 and 7). All regression slopes did not differ significantly from unity.

Discussion

Remarkably, this is the first study to combine these two well-established methods to provide absolute values of MCABF. As there are no significant changes in MCALD during most interventions, a single time-averaged LD measurement by MRA can be used with successive TCD measurements of BV to produce dynamic, absolute values of MCABF.

As with all Doppler approaches to blood flow measurements, many assumptions are made (Gill, 1985). Most are compromised, but are generally acceptable, in hypothesis testing and

some clinical situations. For non-image guided TCD BV measurements, these include, but are not limited to: uniform acoustic beams, zero Doppler angles, blunt velocity profiles, and constant circular cross-sections. Our *in vitro* data with their highly controlled conditions provides evidence for good precision and accuracy in a *best case* scenario. Carefully done, the *in vitro* flow results experimentally confirm both the Doppler equation and the conservation of mass. Thus, strong *in vitro* correlations should be expected and are generally reported. They are necessary, but not sufficient, for future applications.

Alternatively, in subjects with similar age and gender to our study population who are unable to undergo expensive and technically demanding MRA, a standard 0.30 cm (or age and gender adjusted) LD could be used with known, and perhaps, acceptable ranges (Muller et al, 1991). Thus, this nominal value could be used directly to calibrate MCABV into MCABF estimates which may be preferred in some physiological experiments or clinical conditions. To test this approach, we compared our bilateral 70 MCABF values in the 35 adults (with measured MCALD) to calculations assuming a MCALD of 0.30 cm. The correlation coefficient was 0.84 and the slope did not differ significantly from unity. Clearly, estimates of MCABF may complement, not replace, the standard measurements (with less variances) of MCABV and their differences (Bishop 2013). Knowing these uncertainties is also a useful tool in statistical power analysis for interventional studies.

Although human cerebral BF in an individual is generally tightly controlled compared to other vascular beds, the reported ranges of normal, resting values (in ml/min or ml/min/100 grams), regardless of measurement technique, are relatively large (Windermark et al, 2005). Our wide range of MCABF measurements is consistent with the literature (Lin et al, 2001; Sorand et al, 2010). As with others (Macchi and Catini, 1994), we found no significant correlation between MCABF and body weight. This limits possible scaling factors (such as body weight) to decrease the additional measurement variance when LD is used to calculate MCABF from MCABV measurements. Clearly, estimates of MCABF must be balanced with the increase in measurement variance compared to measurements of MCABV (and their percentage changes) alone. Nevertheless, as LD correlates with age and sex, these scaling factors may be possible (Karnik et al, 1996).

Importantly, the spread of our MCALD measurements from MRA is also similar to reported values (Tarasow et al, 2007). Ranges of LD are generally smaller than MCABV. The spatial resolution of MRA is surely challenged at the lower diameter levels (~0.25cm), but the mean/SD values around 0.30/0.03cm are relatively consistent. These data give an estimate of the uncertainties of MCABF calculations if one assumes a LD of 0.30cm. Most other cerebral BF and perfusion measurement techniques also make compromised assumptions and thus have similar variances (Lin et al, 2001, Windermark et al, 2005; Chen et al, 1994).

Initially, this new method would be most useful for cardiovascular and neural physiologists who study moving subjects. Clearly, under most circumstances, investigators and clinicians would prefer absolute BF over BV indices assuming that both are equally precise and accurate. Specifically, the delivery of oxygen and other blood borne masses could be better *estimated*. Given the biological variability and the limitations of measurements of human cerebral BF, it often remains unclear what are normal and abnormal BF ranges. Generally, it

is the spatial or temporal *change* in BF with interventions in a given person that is important as each person serves as their own control. TCD MCABV measurements are very useful here, but again, they are not MCABF. They do not allow mass transport measurements or input functions for estimates of cerebral perfusion.

The clinical usefulness of this technique may be determined in the future. The method may only be applicable in physiological studies where flow regimes are not complicated by turbulent flow patterns, rapidly changing diameters, and complex velocity profiles that are created by diseased and stenotic conduit vessels or significant vasomotor activity and spasm (Purkayastha and Sorond 2013). Our purpose is to present a physiological tool that *may* be useful clinically. This is particularly true in rural and developing countries where low energy, portable, durable, and inexpensive techniques are the only option.

Standard, portable, noninvasive Doppler flow measurements from the internal carotid artery are well validated and can also provide similar cerebral conduit blood flow (Oktar et al. 2006; Scheel et al. 2000a; Scheel et al. 2000b). Their important limitation is that the transducer location and lumen insonation cannot easily be fixed in the neck as it can be with the TCD and its head set on the rigid skull. By keeping the Doppler sample volume and angle constant within the blood vessel, TCD with transducer fixation is necessary in accurate and precise long term monitoring, ambulatory, and exercise studies.

Although we compared proximal ICABF and MCABF, the major limitation of this study is the universal lack of a gold standard for *in vivo* measurements of human MCABF. Nevertheless, MCABF calculated from TCD BV and MRA LD and validated here *in vitro* are physiologically reasonable (~170 ml/min), bilaterally similar, and are consistent with the limited reported alternative measurements and theoretical models (Enzuman et al. 1994; Stock et al. 2000; Zhao et al. 2007; Moore et al. 2006). The strong correlation MCABF and ICABF gives some evidence to the validity of the technique. Nevertheless, it may be compromised by the indeterminate and complex vascular anatomy through the Circle of Wills and between the ICA and middle segment of the MCA (Moore et al, 2006). These arterial outflows are reflected in the differences of the absolute values of MCABF and ICABF (~100 ml/min). We assume that flows in these small arteries are proportional and steady. Furthermore, our *in vitro* and *in vivo* validations suggest relatively good accuracies and precisions for these new, “duplex” measurements of MCABF when compared to our methods.

As portable TCD techniques are relatively inexpensive and wide spread, the cost effectiveness of this approach will depend mostly on the availability, time, and cost of the determination of LD by MRA. Fortunately, LD measurements often can be extracted from standard clinically indicated or IRB approved MRA images with modest additional time and expense.

Conclusions

Our data suggest that independent TCD and MRA measurements of MCABV and MCALD, respectively, can be used with reasonable accuracy and precision to make quantitative

calculations and estimates of MCABF. Clearly, measurements of MCA conduit blood flow are limited when compared to MR measurements of global, regional, and local perfusion. Nevertheless, with the addition of LD values, highly portable, inexpensive, and widely available TCD devices may be calibrated from blood *velocity* into blood *flow* thus increasing its usefulness in *monitoring* transport phenomenon into the human brain under a wide spectrum of conditions.

Acknowledgements

We thank Heather Jensen, Chris Dee, Julia Middendorf, Adrian Carter, and Chuck Gasparovic PhD for their technical help.

Grant support

This research was funded by the grant RO1-HL04722-01-A6 by the National Institutes of Health/National Heart Lung and Blood Institute and in part by the grant 8UL1-TR000041 by the National Center for Research Resource

References

- Arnolds BJ, von Reutern GM. Transcranial Doppler sonography: Examination technique and normal reference values. *Ultrasound Med Biol*. 1986; 12(2):115–123. [PubMed: 2943067]
- Bishop CC, Powell S, Rutt D, Browse NL. Transcranial Doppler measurement of middle cerebral artery blood flow velocity: A validation study. *Stroke*. 1986; 17(5):913–915.
- Bishop DV. Cerebral asymmetry and language development: cause, correlate, or consequence. *Science*. 2013; 340:6138.
- Chen JJ, Wieckowska J, Meyer E, Pike GB. Cerebral blood flow measurements using MRI and PET: a cross - validation study. *Int J Biomed Imaging*. 2008;516359. [PubMed: 18825270]
- Enzmann D, Ross M, Marks M, Pelc N. Blood flow in major cerebral arteries measured by phase-contrast cine MR. *AJNR*. 1994; 15:123–129. [PubMed: 8141043]
- Eriksen M. Effect of pulsatile arterial diameter variations on blood flow estimated by Doppler ultrasound. *Med Biol Comput*. 1992; 30:46–60.
- Gill RW. Measurement of blood flow by ultrasound: accuracy and sources of error. *Ultrasound Med Biol*. 1985; 11:625–641. [PubMed: 2931884]
- González-Alonso J, Dalsgaard MK, Osada T, Volianitis S, Dawson EA, Yoshiga CC, Secher NH. Brain and central haemodynamics and oxygenation during maximal exercise in humans. *J Physiol*. 2004; 557(Pt 1):331–342. [PubMed: 15004212]
- Greene ER. Noninvasive transthoracic and transesophageal Doppler echocardiographic measurements of human coronary blood velocity: In vitro flow phantom validation. *Proceedings of IEEE/EMB*. Aug.2010 :3784–3787.
- Hatab MR, Giller CA, Clarke GD. Evaluation of cerebral arterial flow with transcranial Doppler ultrasound: theoretical development and phantom studies. *Ultrasound Med Biol*. 1997; 23(7): 1025–31. [PubMed: 9330446]
- Hellsstrom G, Fisher-Colbrie W, Wahlgren NG, Jogestrand T. Carotid artery blood flow and middle cerebral blood flow velocity during physical exercise. *J Appl Physiol*. 1996; 81:413–8. [PubMed: 8828693]
- Lin W, Celik A, Derdeyn C, Hongyu A, Lee Y, Videen T, Ostergaard L, Powers WJ. Quantitative measurements of cerebral blood flow in patients with unilateral carotid occlusion: a PET and MR study. *J Mag Res Imag*. 2001; 14:659–667.
- Karnik R, Valentin A, Benedikt-Winkler W, Khaffa N, Donath P, Slang J. Sex-related differences in acetazolamide induced cerebral vasomotor reactivity. *Stroke*. 1996; 27:56–58. [PubMed: 8553403]
- Krabbe-Hartkamp M, van der Grond J, de Leeuw FE, de Groot JC, Algra A, Hillen B, Breteler M, Mali W. Circle of Willis. Morphological variation on three-dimensional time-of-flight MR angiography. *Radiology*. 1998; 207:103–111. [PubMed: 9530305]

- Kremkau, FW. Diagnostic Ultrasound: Principles and Instruments. 4th Edition. WB Saunders; Philadelphia: 1993.
- Lipsitz LA, Mukai S, Hamner J, Gagnon M, Babikian V. Dynamic regulation of middle cerebral artery blood flow velocity in aging and hypertension. *Stroke*. 2000; 31(8):1897–903. [PubMed: 10926954]
- Lyngeraa TS, Pedersen LM, Mantoni T, Belhage b, Rasmussen LS, van Lieshout JJ, Pott FC. Middle cerebral artery blood velocity during running. *Scand J Med Sci Sports*. 2012; 10:1–6.
- Macchi C, Catini C. The measurement of the caliber and blood-flow velocities of arteries of the Circle of Willis: a statistical investigation of 120 living subjects using transcranial color-coded Doppler ultrasonography. *Ital J Anat Embryol*. 1994; 99:9–16. [PubMed: 7755447]
- Martin PJ, Evans DH, Naylor AR. Transcranial color-coded sonography in basal cerebral circulation. *Stroke*. 1994; 25:390–396. [PubMed: 7905680]
- Mitsis GD, Zhang R, Levine BD, Tzanalaridou E, Katritsis DG, Marmarelis VZ. Autonomic neural control of cerebral hemodynamics. *IEEE/EMB*. 2009; 28(6):54–62.
- Moore S, David T, Chase JG, Arnold J, Fink J. 3D models of blood flow in the cerebral vasculature. *J Biomechanics*. 2006; 36:1454–1463.
- Muller HR, Brunhulez C, Radu EW. Sex and side differences of cerebral arterial caliper. *Neuroradiology*. 1991; 33:212–216. [PubMed: 1881537]
- Newell DW, Gomez CR, Babikian VL, Lefkowitz D, Goldman RS, Armon C, Hsu CY, Goodin DS. Assessment: Transcranial Doppler ultrasonography: report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. *Neurology*. 2004; 62:1468–1481. [PubMed: 15136667]
- Nichols, WW.; O'Rourke, MF. MacDonald's Blood Flow in Arteries: Theoretical, Experimental, and Clinical Principles. Arnold Publishers; London: 1998.
- Oktar SO, Yücel C, Karaosmanoglu D, Akkan K, Ozdemir H, Tokgoz N, Tali T. Blood-flow volume quantification in internal carotid and vertebral arteries: comparison of 3 different ultrasound techniques with phase-contrast MR imaging. *AJNR*. 2006; 27(2):363–369. [PubMed: 16484412]
- Özsarlak Ö, Goethem J, Maes M, Parizel P. MR angiography of the intracranial vessels: technical aspects and clinical applications. *Neuroradiology*. 2004; 46:955–972. [PubMed: 15580489]
- Panerai RB. Transcranial Doppler for evaluation of cerebral autoregulation. *Clin Auto Res*. 2009; 19:197–211.
- Poulin MJ, Robbins PA. Indexes of flow and cross-sectional area of the middle cerebral artery using doppler ultrasound during hypoxia and hypercapnia in humans. *Stroke*. 1996; 27(12):2244–2250. [PubMed: 8969788]
- Purkayastha S, Sorundi E. Transcranial Doppler ultrasound: technique and application. *Semin Neurol*. 2013; 32:411–420. [PubMed: 23361485]
- Ramnarine KV, Nassiri DK, Hoskins PR. Validation of a new blood-mimicking fluid for use in Doppler flow test objects. *Ultrasound Med Biol*. 1998; 24(3):451–459. [PubMed: 9587999]
- Rosset A, Spadola L, Ratib O, OsiriX. An open-source software for navigating in multidimensional DICOM Images. *J Digital Imaging*. 2004; 17(3):205–216.
- Ruggieri P, Laub G, Masaryk T, Modic M. Intracranial circulation: pulse-sequence considerations in three-dimensional (volume) MR angiography. *Radiology*. 1989; 171:785–791. [PubMed: 2717753]
- Scheel P, Ruge C, Petruch UR, Schöning M. Color duplex measurement of cerebral blood flow volume in healthy adults. *Stroke*. 2000a; 31(1):147–150. [PubMed: 10625730]
- Scheel P, Ruge C, Schöning M. Flow velocity and flow volume measurements in the extracranial carotid and vertebral arteries in healthy adults: reference data and the effects of age. *Ultrasound Med Biol*. 2000b; 26(8):1261–6. [PubMed: 11120363]
- Schoning M, Scheel P. Color duplex measurement of cerebral blood flow volume: intra- and interobserver reproducibility and habituation to serial measurements in normal subjects. *J Cereb Blood Flow Metab*. 1996; 16:523–531. [PubMed: 8621758]
- Schreiber SJ, Gottschalk S, Weih M, Villringer A, Valdueza JM. Assessment of blood flow velocity and diameter of the middle cerebral artery during the acetazolamide provocation test by use of

- transcranial Doppler sonography and MR imaging. *AJNR*. 2000; 21:1207–1211. [PubMed: 10954270]
- Serrador JM, Picot PA, Rutt BK, Shoemaker JK, Bondar RL. MRI measures of middle cerebral artery diameter in conscious humans during simulated orthostasis. *Stroke*. 2000; 31(7):1672–1678. [PubMed: 10884472]
- Sorond F, Hollenburg NK, Panych LP, Fisher ND. Brain blood flow and velocity: correlations between magnetic resonance imaging and transcranial Doppler. *JUM*. 2010; 29:1017–1022.
- Soustiel JF, Glenn TC, Vespa P, Rinsky B, Hanuscin C, Martin NA. Assessment of cerebral blood flow by means of blood-flow-volume measurement in the internal carotid artery: comparative study with a 133xenon clearance technique. *Stroke*. 2003; 34(8):1876–1880. [PubMed: 12843349]
- Stock KW, Wetzel S, Kirsch E, Bongartz G, Steinbrich W, Radue EW. Anatomical evaluation of the circle of Willis: MR angiography versus intraarterial digital subtraction angiography. *AJNR*. 1996; 17:1495–1499. [PubMed: 8883648]
- Stock KW, Wetzel SG, Lyrer PA, Radü EW. Quantification of blood flow in the middle cerebral artery with phase-contrast MR imaging. *European Radiology*. 2000; 10(11):1795–1800. [PubMed: 11097408]
- TarasÓw E, Ali AAS, Lewszuk A, Walecki J. Measurements of the middle cerebral artery in digital subtraction angiography and MR angiography. *Med Sci Monit*. 2007; 13(Suppl 1):65–72. [PubMed: 17507888]
- Valdúeza JM, Balzer JO, Villringer A, Vogl TJ, Kutter R, Einhüpl KM. Changes in blood flow velocity and diameter of the middle cerebral artery during hyperventilation: Assessment with MR and transcranial Doppler sonography. *AJNR*. 1997; 18:1929–1934. [PubMed: 9403456]
- Windermark M, Sesay M, Barbier E, et al. Comparative overview of brain perfusion imaging techniques. *Stroke*. 2005; 36:e83–e99. [PubMed: 16100027]
- Zhang R, Zuckerman JH, Giller CA, Levine BD. Transfer function analysis of dynamic cerebral autoregulation in humans. *Am J Physiol*. 1998; 274(1 Pt 2):H233–241. [PubMed: 9458872]
- Zhao M, Amin-Hanjani S, Ruland S, Curcio AP, Ostergren L, Charbel FT. Regional cerebral blood flow using quantitative MR angiography. *AJNR*. 2007; 28:1470–1473. [PubMed: 17846193]

Figure 1.

Top: 2D image slice produced by MRA. This typical image was used for LD determination by electronic calipers, which provide absolute values in cm within the DICOM viewing software. Overlaid is schematic of the TCD insonation of the middle section of the MCA. Left: 3D representation compiled from the multiple 2D MRA slices from which the MCA was identified and isolated. Right: Doppler spectral waveforms created by TCD for BV determinations from the spectral envelopes.

Figure 2.

Bilateral BV, LD, and BF data (35 subjects, 70 MCA vessels) plotted as the mean with two-tailed SD bars. The means/SD are: BV left: 42.7 $\pm$ 14.7cm/s, right: 42.5 $\pm$ 14.3cm/s; LD left: 0.29 $\pm$ 0.04cm, right: 0.30 $\pm$ 0.03cm; BF left: 168 $\pm$ 72ml/min, BF right: 180 $\pm$ 69ml/min.

There were no significant differences bilaterally in any of the variables.

Figure 3.
Bilateral correlation of right and left BF in both the MCA and ICA in 16 adults.

Figure 4.
In vitro precision with correlation of 30 repeated measurements of MCABF in the flow phantom

Figure 5.

In vitro accuracy with correlation of 30 paired measurements of phantom time collection and MCABF with TCD BV and caliper measurements of LD (0.40 cm)

Figure 6.

In vivo precision with correlation of 16 repeated measurements of MCABF in 16 adults

Figure 7.

In vivo accuracy with correlation of left and right ICABF and MCABF in 16 adults. Note higher ICABF values (~100 ml/min) due to outflows proximal to the MCA.