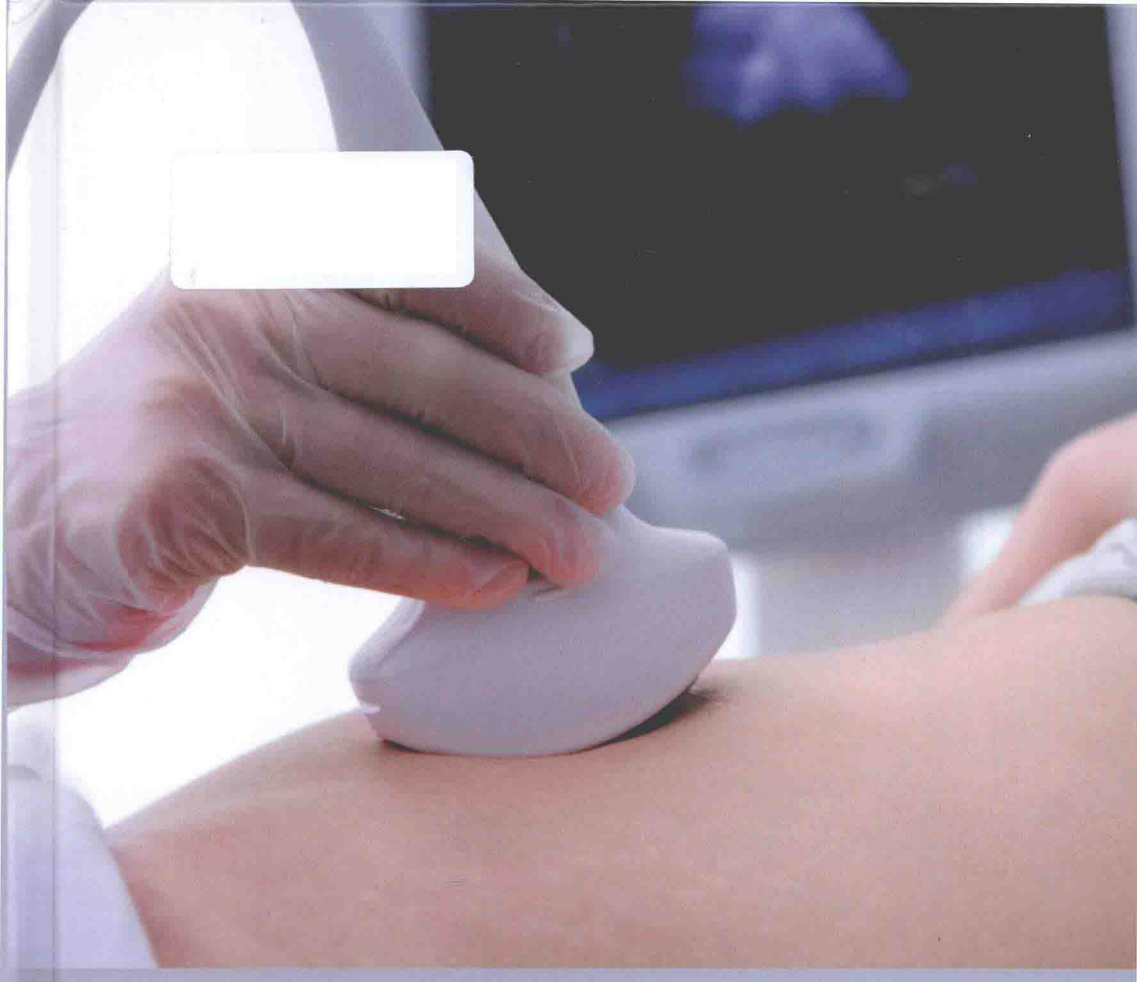

Principles and Applications of Ultrasonography in Humans

Kristen Bone

Principles and Applications of Ultrasonography in Humans

Edited by **Kristen Bone**

hayle medical
New York

Published by Hayle Medical,
30 West, 37th Street, Suite 612,
New York, NY 10018, USA
www.haylemedical.com

Principles and Applications of Ultrasonography in Humans
Edited by Kristen Bone

International Standard Book Number: 978-1-63241-326-0 (Hardback)

Printed in China.

Principles and Applications of Ultrasonography in Humans

Preface

Every book is initially just a concept; it takes months of research and hard work to give it the final shape in which the readers receive it. In its early stages, this book also went through rigorous reviewing. The notable contributions made by experts from across the globe were first molded into patterned chapters and then arranged in a sensibly sequential manner to bring out the best results.

This book presents an extensive insight into various applications of ultrasonography in medical science and associated domains. Compiled with contributions from international experts, it offers the readers with current information and future research pathways of diagnostic and therapeutic ultrasound and spectroscopy. Major topics comprise of Duplex ultrasound, transcranial color Duplex, MRA guided Doppler ultrasonography and near-infrared spectroscopy. The applications of ultrasound for the discovery of intra-cardiac and intra-pulmonary shunts have also been explained along with its utility for the assessment of gastric regulation and emptying in the book. New directions in the use and application of transcranial and color Duplex ultrasound have also been presented, along with the use of ultrasound and arterial stiffness for measuring human vascular health and circulatory control.

It has been my immense pleasure to be a part of this project and to contribute my years of learning in such a meaningful form. I would like to take this opportunity to thank all the people who have been associated with the completion of this book at any step.

Editor

Contents

1

Theory and Practice of MRA-Guided Transcranial Doppler Sonography

Francisco L. Colino and Gordon Binsted
Department of Human Kinetics, Faculty of Health and Social Development, The University of British Columbia, Kelowna, BC, Canada

1. Introduction

Despite consisting of 2 - 3% of total body mass, the brain accounts for ~20% of the body's oxygen consumption and therefore must receive significant blood supply to maintain homeostasis (Ainslie & Duffin, 2009). This profound dependency on blood supply belies the brain's apparent ability to regulate blood supply so tightly. Hence, the brain's ability to regulate its blood supply has been, and still is, the subject of considerable research (e.g., Kety & Schmidt, 1948; Panerai et al., 2009; Willie & Smith, 2011; Willie et al., 2011; also see Ainslie & Duffin, 2009 for a recent review). However, the dense cortical bone of the skull does not lend itself easily to normal ultrasound techniques.

The most common tool for assessing cerebral blood flow regulation is transcranial Doppler sonography (TCD) as it operates at lower frequencies (usually 1 - 2 MHz), relative to conventional ultrasound frequencies (≥ 5 MHz), to penetrate the skull. Traditionally, researchers rely solely on an M-mode display[1] for information regarding depth, blood flow velocity, pulsatility index, etc. (Aaslid et al., 1986). Based on historical indicators they infer which vessel is insonated; for example, the user can perform simple stimulus-response tests to confirm that the identity of the vessel. A reduction in blood flow velocity following the vibration/compression of the external carotid would confirm middle cerebral artery (MCA) insonation. In a similar fashion, flow variation accompanying the opening/closing of the eyes is a simple confirmatory test for the posterior cerebral artery (PCA).

Despite these well-established procedures to determine vessel identity, there are several notable problems with the current approach. First, TCD measures blood flow velocity, which is a relative measure; absolute flow cannot be estimated without knowing the vessel diameter. Specifically, according to Poiseuille's Law, flow (Q) is determined by the vessel length (L), pressure difference (P), viscosity (η) and, most notably, vessel radius (α).

$$Q = \frac{pa^4 P}{8Lh} \tag{1}$$

[1] M-mode stands for 'motion mode'. This modality returns echoes over time for one line of the B-mode image. Thus, movement of structures positioned in that line can be visualized in a time-varying fashion. Often M-mode and B-mode are displayed together on the ultrasound monitor.

While each factor is relevant to an accurate estimate of flow, vessel radius has the most profound influence as it is raised to the fourth power. For example, if an occlusion (e.g., due to thrombus etc.) decreases vessel radius by 1/2 then blood flow decreases 16-fold. Thus, it is critical to know the *veridical* radius when estimating absolute volumetric flow – even if the other factors are known.

However, it is also important to note that intracranial arteries are distensible (Monson et al. 2008) and therefore the reliance on Poiseuille's Law is inappropriate. Notably, a recent computer simulation of the cerebral circulation has identified vascular compliance as an important determinant of dynamic cerebral pressure–flow relationships characterized in the frequency domain (Zhang et al. 2009). Based on a Windkessel model, they reported that increases in steady state cerebrovascular resistance and or decreases in compliance could alter dynamic pressure–flow velocity relations within the cerebral circulation. This finding suggests added complexity to the study of cerebrovascular physiology because the current characteristics, derived largely from transfer function analysis (TFA), are commonly ascribed to active vascular control mechanisms without acknowledging the dynamic mechanical properties of the cerebral vasculature. Specifically, vascular compliance necessitates the consideration of the rate of pressure change driving the volume expansion in compliant vessels (i.e. capacitive blood flow) in addition to the instantaneous blood pressure that drives blood flow directly through small resistive vessels (Chan et al. 2011).

When estimating blood flow velocity using TCD, insonation angle can also profoundly impact measure accuracy. The accuracy of the flow-measure estimate increases as the insonation angle decreases (i.e. becomes closer to parallel). An oblique angle results in underestimation (see Aaslid, 1986). Problematically however, information regarding insonation angle is rarely available. Indeed, blood velocity data garnered from TCD are often compared to control conditions using percent change metric as an attempt to control for this shortcoming. Such an approach makes comparison between individuals and/or groups problematic at best. Information regarding vessels course, depth and diameter would reasonably aid estimation of absolute blood flow, while confirmation of insonation location (e.g., segment of vessel) and insonation angle will aid replication and reliability. Thus, with this knowledge, researchers would be able to employ more varied designs, enabling consideration of absolute, multi-day measures and between-subject comparisons. While we certainly acknowledge that the majority of TCD users adopt attenuation methods as opposed to absolute velocities (for the reasons highlight above), it is nonetheless important to recognize the limitations of stimulus-response relationships (e.g., for reactivity or autoregulation testing. read: Ainslie & Duffin; and Willie et al) and present more comprehensive alternatives.

There are limited number of examples in the literature exist that attempted to address the problem of TCD guidance (Auer et al., 1999; Kantelhardt et al., 2011). A recent study looked at neurological patients with various forms of head trauma using computerized tomography of the basal cerebral arterial architecture (Kantelhardt et al., 2011). These authors demonstrated that CT-guided TCD is a viable and efficient means to re-examine neurology patients. Specifically, this group was able to reduce initial examinations to approximately 8 minutes of all measured vessels (i.e., internal carotid artery, MCA, MCA bifurcation, PCA, anterior cerebral artery (ACA), and posterior communicating arteries). Kantelhardt and colleagues concluded that navigated TCD provides faster and more reliable insonation of all

basal cerebral vessels given visualized anatomical references. Incredibly, subsequent examination times on the same patient were reduced by approximately 50%. The development of a standardized protocol for image-guided TCD, to establish spatial coordinates of vascular structures, should aid multi-day investigations by improving inter-session precision, reducing inter- and intra-investigator variability, and accommodating cases of atypical vascular architecture.

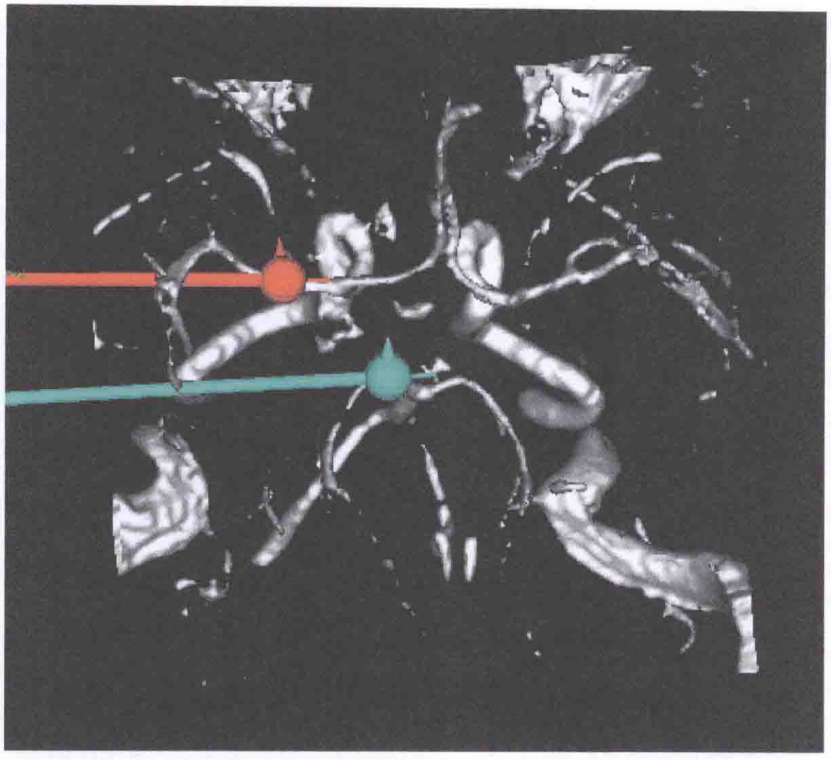

Fig. 1. Example of targets on MCA (red trajectory) and PCA (light blue trajectory) for TCD guidance. The experimenter is guided to the target vessel relative to the targets set by the experimenter. The angle of the probe relative to the these target gives insonation angle as well as target depth. However, it is important to note that target selection is entirely based on experimenter judgment. Therefore, it is recommended that the target is set as parallel as possible to the blood vessel's longitudinal axis. Indeed, a tortuously coursed vessel complicates the procedure.

The limitations presented for TCD stem largely from its inability, due to low ultrasonic frequency, to resolve a useful 2D image. Higher ultrasound frequencies cannot adequately penetrate the bones of the skull. B-mode duplex ultrasonography used in neurosurgical settings (e.g., Mathiesen et al., 2007; Mercier et al., 2010; Weiss et al., 2008) is only possible due to the availability of an open window free of boney obstruction. In most physiological experiments the researcher does not have this luxury and are limited to relying on "windows" (i.e., areas of thin bone) to interrogate the vessels of interest (Grolimund, 1986). A way to overcome this physical barrier is achieved by magnetic resonance angiography

(MRA) which, when coupled with existing neuronavigation systems (Gronningsaeter et al., 2000; Mathiesen et al., 2007), can provide an effective means to help direct the TCD probe. While there are other imaging modalities in available (e.g., CT), MRA is a non-invasive method that does not emit ionizing radiation nor does it require contrast agents (Kantelhardt et al., 2011).

2. Magnetic Resonance Angiography: Basic principles

Magnetic resonance angiography (MRA) uses a combination of static magnetic fields and radiofrequency pulses to generate images that can readily be used to assess the cerebral arteries and veins (Wedeen et al., 1985). Tissues have inherent magnetic relaxation times (e.g., T_1, T_2) that principally determine how they appear in an image. Blood has a long T_1 relaxation time (~1.2 secs), which is exploited to generate MR angiograms. A typical MRA image acquisition utilizes the "time-of-flight" (TOF) imaging method whereby (in one variant) the flow of blood from one position to the next will change the returned signal, thus differentiating blood from stationary tissues. Conventional spin-echo and fast spin-echo images result in "dark blood" (i.e., flowing blood returns no signal and, therefore, appears dark), however researchers interested in the arteries themselves often seek images via a gradient-echo pulse sequence. Unlike spin-echo or fast spin-echo sequence, only one radiofrequency pulse is emitted during each repetition cycle to negate the image wash-out (Edelman & Meyer, 2003). The resulting angiograms are referred to as "bright blood" images because the blood in the cerebral vessels returns much more signal than the surrounding tissue. In general, three-dimensional TOF MRA is best for high anatomical resolution, whereas two-dimensional TOF MRA is best to image slow or turbulent blood flow (Baumgartner et al., 1995). Thus, three-dimensional TOF MRA is most appropriate for TCD navigation.

MRA-guided duplex ultrasound has been used in neurosurgical settings (Akdemir et al., 2007; Mathiesen et al., 2007), but transcranial examinations are of limited use because of the acoustic windows of the skull (Baumgartner et al., 1995; Gerriets et al., 1999; Grolimund, 1986). Similarly then, MRA-guided TCD can reduce search times dramatically and improve examiner anatomical orientation (Kantelhardt et al., 2011) with several examples commercially packages available[2]: Kolibri navigation system (Softouch, Brainlab AG), Brainsight 2 (Rogue Research). Once the images are collected and downloaded into the guidance software, a threshold-based segmentation of the arteries from the surrounding tissue and three-dimensional reconstruction must be performed (Figure 1). A 3D reconstruction of the vascular architecture that is spatially matched with a subject's anatomical MRI image provides a virtual representation for easy vessel identification and ultrasound interrogation. Further, based on this abstraction, the experimenter can calculate vessel diameter and insonation angle (discussed below).

The above guidance systems use frameless image guidance. The use of passive infrared tracking systems in combination with a relative guidance coordinate system permits subjects to move freely (see Figure 2). In general, the registration process begins with the

[2] These systems are employable with some modification. No system is natively able to physically accommodate a TCD probe nor optimally configured to target Doppler signal.

acquired MRA image and identifying anatomical landmarks in the guidance software (e.g., tip of the nose, nasion, left and right inter-tragal notch) and the registration of these fiducial landmarks. Rigid bodies are fixed to the subject and the TCD probe and co-registered (Figure 2). While this approach to image guidance for TCD has shown to dramatically improved acquisition of circle of Willis arteries (Auer et al., 1999; Kantelhardt et al., 2011), this data does not speak to the accuracy of tracking the subject and tool.

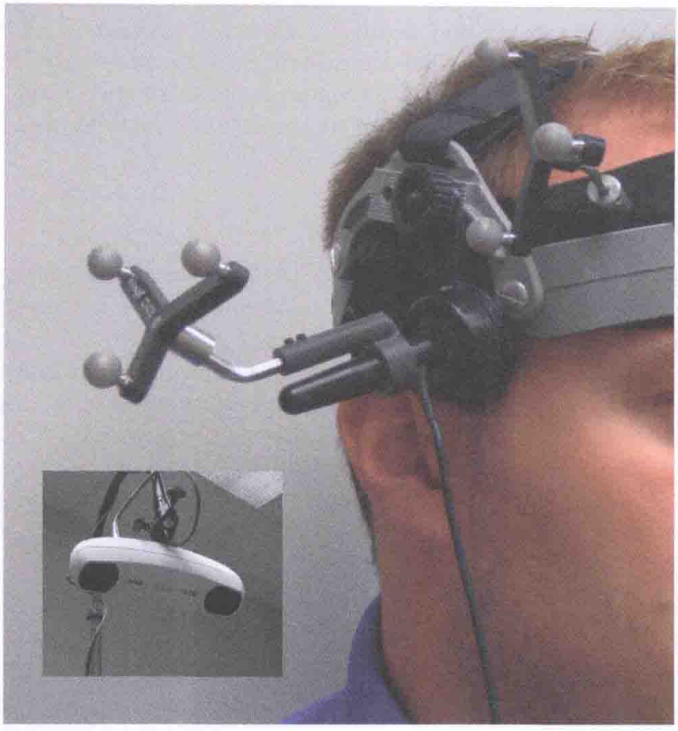

Fig. 2. Rigid bodies attached to example participant's head to track the three-dimensional position of the TCD probe relative to the participant's head. The rigid bodies are tracked by an infrared-emitting camera (inset; Polaris Vicra IR camera, Northern Digital Inc., Waterloo, ON, Canada) that emits IR light that reflects back to the camera by the passive IR markers fixed to each rigid body. Pictured is a TCD probe, a MARC 600 head mount (Spencer Technologies, Seattle, WA, USA) and rigid bodies (Brainsight, Rogue Research, Montreal, QC, Canada).

3. Measurement errors and insonation angle

Despite image guidance's utility, using rigid body reconstructions to track tools (i.e., markers attached to the TCD probe and the subject in this case) has inherent uncertainty. This is particularly concerning when an experimenter attempts to acquire a deep vessel (e.g., middle cerebral artery). Most motion capture manufacturers claim sub-millimeter precision performance of their products, however the published errors assume measurements are taken at the rigid body (see Figure 2). For the purposes of TCD it is useful to consider the minimum tracking uncertainty as expressed as per unit insonation depth. As exemplar,

consider a camera system with a volume accuracy of 0.25 mm with a 0.5 mm confidence interval. That is, the tool being tracked can be tracked to the nearest 0.25 mm with an uncertainty of 0.5 mm (*N.B.* these numbers describe the Polaris Vicra, Northern Digital Inc. To view these specifications, see http://www.ndigital.com/medical/polarisfamily-techspecs.php). Further, the rigid body tracking the TCD probe is 8 cm long and the skin-to-skull distance is 0.25 cm. Thus, we can calculate the "tracking uncertainty" using simple trigonometry; the result of which gives $x \approx 0.63$ mm of error for every 10 mm of insonation depth. Thus, with a 50 mm insonation depth generates approximately 5.8 mm of tracking uncertainty. Therefore every researcher considering using image-guiding systems for experiments must keep in mind when designing an experiment and taking measurements. Let us review the calculations and point out important variables that affect tracking uncertainty.

3.1 Estimating insonation angle

Classically, the insonation angle is unknown in TCD-based vascular experiments. This leads to uncertainty as to how much velocity measurements are underestimated during measurement. Also, we already know from the physics of Doppler shifts (see Aaslid, 1986 for a complete review of the physics behind Doppler shift in blood velocity measurement) that the higher the degree of perpendicularity to the signal of interest, the higher the degree of underestimation. Indeed, when insonating a vessel an observer who is not aware of this potential issue can mistakenly take the observed blood velocity as the true blood velocity when, in fact, observed blood velocity may be much lower than that observed (Aaslid, 1986). Specifically,

$$v = |v'| \cos\sigma \tag{2}$$

where v is observed blood velocity, v' is the true blood flow velocity, and σ is the angle of the ultrasonic beam relative to the flow vector (i.e., insonation angle). However, it is unlikely that insonation angle is zero for any given TCD measurement. Almost more importantly however, the experimenter does not know the insonation angle and, therefore, does not know by how much blood velocity is underestimated. For example, we have observed insonation angles as great as 30° while interrogating the posterior cerebral artery (PCA) while observing an average blood velocity of 55 cm/sec (unpublished observations). The observed blood velocity is therefore underestimated by approximately 14% and the absolute blood velocity is approximately 64 cm/sec. However, researchers must keep in mind that a relatively perpendicular insonation angle may be the only approach to insonate an artery given the limitations imposed by the temporal acoustic window.

4. Measuring temporal bone thickness

The cranial bones are made up of three layers; each influences the ultrasound beam in a different way (White et al., 1978). In most cases however, ultrasonic power is markedly reduced by transmission through the temporal bone. Power loss is primarily a function of bone thickness as long as the bone is structurally homogeneous (i.e., no thickness variation). If the temporal bone thickness varies, the bone acts as an acoustic lens by scattering the acoustic energy across space (Grolimund, 1986). Nontheless, researchers should be aware

that increased bone thickness impedes TCD measurements. Insonating at an angle that is normal (i.e., 90 degrees) to the bone diminishes boney impediment to the ultrasound beam (Ammi et al., 2008). Furthermore, possessing a library of anatomical MRI images that can be acquired with an MRA, from subjects opens the possibility for screening subjects for adequately thin acoustic windows.

Bone thickness, for the purpose of TCD, can be estimated at the temporal bone rostral to the ear and dorsal to the zygomatic arch using any standard MRI imaging software (e.g., Osirix). The experimenter can therefore judge variations in the temporal acoustic window by measuring thickness of the cortical bone in sequential order from the point where the zygomatic arch meets the ear dorsally and rostrally. Grolimund (1986) observed that cortical bone in the temporal acoustic window as thin as 2.5 mm resulted in 99% energy loss in the ultrasound beam, as well as significant scattering of the beam (Ammi et al., 2008; Grolimund et al., 1986). Measuring the borders of the temporal acoustic window can assist experimenters to visualize it appropriately. Thus, they can determine the best approach to the cerebral vessels given the acoustic constraints provided by a subject's anatomy. Also, knowing the window boundaries can help reduce experiment time by eliminating the need to reposition the TCD probe during vessel acquisition.

Having a defined acoustic window can inform experimenters how to optimally approach a blood vessel by maximizing signal and reducing insonation angle. Unfortunately, for some subjects the available acoustic window may not afford a good approach to underlying vessels. In other words, the approach that optimizes insonation angle may not be optimal for good signal acquisition. Indeed, in our laboratory we observed maximum signal from the PCA was reached with an insonation angle > thirty degrees. However, when the probe was adjusted for optimal insonation angle ($< 5°$) the signal quality suffered severely due to bone occlusion. That is, the image guiding system confirmed that the probe was pointed at the PCA but there was insufficient signal from the PCA for any useful analysis (unpublished observations).

Certainly, these observations demonstrate the inherent drawback of insonating through bone - signal will always be lost and in some cases, completely. Indeed, in a recent study Ammi et al. (2008) conducted a study of ultrasound beam penetration through human skull specimens. They found that all ultrasonic pulses sent from various ultrasonic emitters of differing frequencies (i.e., 1.03 and 2.0 MHz) were attenuated as a function of bone thickness. Furthermore, sound pressure level of a 2.0 MHz probe, measured by a hydrophone, was diminished by more than 75% at the location they calculated the MCA would be *in vivo* (for details on this hydrophone alignment procedure see Ammi et al., 2008, *pp.* 1581-2). Thus, despite the informative benefits of using an imaging system for experimental optimization, these results highlight the fact that no guidance system can overcome the physical barrier of the temporal bone.

5. MRA and TCD vessel diameter measurement: Method agreement

We mentioned in the introduction that the brain requires an adequate supply of oxygen to maintain normal functions (Ainslie & Duffin, 2009), and the methods by which the brain does this is difficult to determine without a reliable estimate of absolute blood flow, and therefore vessel diameter. Due to obvious physical and ethical limitations, indirect measures must be

employed leaving the true value of a physiological quantity unknown. Generally, new measures are compared against a "gold standard" method to assess the newer measure's reliability, or, in other words, quantify measurement error (Atkinson & Nevill, 2006). Atkinson & Nevill (1998) defined reliability as "the amount of measurement error that has been deemed *acceptable for the effective practical use* of a measurement tool" (emphasis added). It is important to note that it is inevitable that different measures will have a degree of disagreement but it is important to measure *how much* disagreement exists between two measures (Bland & Altman, 1999) the impact of this difference. In the context of this review, the methods of interest are TCD and MRA and the practical impact on flow estimates was considered.

In a recently published study, Wilson et al. (2011) compared vessel diameter measurements from transcranial color Doppler ultrasound (TCCD) and MRA. In brief, they correlated transcranial Doppler and MRA vessel diameter estimates and found them to correlate (Pearson's $r = 0.82$, $r^2 = 0.67$). The robustness of this correlation superficially suggests a degree of confidence can be had in TCD estimates, as they appear to correspond well to MR values. However, the Wilson et al. (2011) study only included 7 subjects in their comparison between TCCD and MRA diameter comparisons (although it must be noted that this was *not* the primary research question of Wilson et al., 2011). Atkinson and Nevill (2006) suggest that 40 participants is the minimum number required to perform a measurement comparison study. As such, this correlation should be interpreted with caution, due to insufficient power, however it would similarly be inappropriate to discount it, as the data appear externally valid.

Despite a strong correlation, the presence of systematic bias between the TCD and MRA methods was not addressed by Wilson et al (2011). What is immediately apparent is from their data (see Table 1) is that TCCD vessel diameters generally larger than the MRA-derived diameters. Plotting these differences using a Bland-Altman approach (Figure 3) reveals clear systematic bias in which the ultrasound-derived vessel diameters are nearly twice those measured from MRA. Proportional bias is also evident whereby systematic differences between method sensitivities across the measurement range (Atkinson & Nevill, 2006). We can further assess measurement differences by determining their limits of agreement (LOA). The LOA expresses maximum deviation between any two repeated observations with a 95% certainty. Notably, a sizeable proportion of the data lies above the upper limit of agreement ($LOA_{upper} = 3.23$; $LOA_{lower} = 2.04$), indicating poor agreement between MRA and TCCD. However, in the present case of due to the proportional bias present in this data LOA should be interpreted with caution for determination of agreement between TCCD and MRA vessel measurements (Bland & Altman, 1999). A similar caution should be taken when considering intraclass correlation coefficients for the same purpose, as they too assume no relationship between error and magnitude of a measured value.

Fortunately, the proportional biases in TCCD/MRA reliability can be corrected using a logarithm transformation of the raw data (see Table 2). The log-transformed differences can be plotted (Figure 4) and thus permit the LOA to be determined for this bias-free data (see Table 2). LOA for the log-transformed data show that the two methods appear to agree fairly well; data points fall within the limits of agreement ($LOA_{upper} = 0.71$; $LOA_{lower} = 0.50$). However, once again, given that these results are derived from a sample of seven participants they must be interpreted with reservation (for a summary of results from other studies, see Table 3).