UNCERTAINTY QUANTIFICATION FOR CEREBRAL PERFUSION

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ABSTRACT
There is a pressing need for noninvasive and continuous measurements of cerebral blood flow (CBF) in several areas of medicine. Transcranial Doppler (TCD) technology is clinically used for measurements of blood flow velocities (BFV). It is assumed that perfusion and vasoreactivity in a vascular territory can be inferred from BFV measurements in the corresponding stem artery. However, only very modest correlations have been found between TCD-based and magnetic resonance imaging (MRI)-based CBF measurements. Several factors, whose values are uncertain, such as vessel diameter, hematocrit and insonation angle, affect the BFV - CBF relationship. Their influence on CBF and vasoreactivity estimates has not been rigorously analyzed but cannot be ignored. We present initial work toward a subject specific computational and experimental model to both quantify and reduce the uncertainty attached to CBF and vasoreactivity estimates based on Doppler ultrasound.

Keywords: uncertainty quantification, perfusion, transcranial Doppler, mathematical modeling

1. INTRODUCTION

Clinical researchers often have to rely on TCD to address questions about rapid CBF regulation and vasoreactivity. However, in spite of long term use, obvious needs and recent advances, further expansion of the TCD methodology in clinical care is impeded by uncertainties inherent to the approach: insonation angles, vessel diameter, skull thickness , blood rheology or even topology of the main cerebral arteries are only approximately known. While the impact of these uncertainties has yet to be fully analyzed, our preliminary studies show the link between measured BFV in main arteries and perfusion or vasoreactivity to be only tenuous.

Magnetic resonance based methods such as Continuous Arterial Spin Labeling (CASL) allow for noninvasive CBF measurements and assessments of regional vascular reactivity; anatomical measurements can also be co-registered. Unlike TCD, they have significant practical limitations: (i) they cannot be used for continuous CBF monitoring at bedside, (ii) recordings need to be averaged thus limiting time resolution, (iii) they cannot be used for studies involving postural challenges, (iv) they are costly and (V) have their own limitations i.e. normalization procedures to a standard space, T1 effects and blood rheology effects and need for contrast agents to increase signal to noise ratio. Therefore, bypassing the above bottleneck for the TCD methodology is of fundamental practical importance.

Computational modeling has been successful at predicting local blood flow (for instance in the presence of aneurysms) for "generic" patients, see e.g. Castro et al. (2009), Greenberg et al. (2009), Kim et al. (2009), Kleinstreuer et al. (2007), Watton et al. (2009). Due to their complexity, these approaches do not easily lend themselves to patient specific predictions or to statistical studies which may require large numbers of runs. In other words, it is difficult in that framework to make judicious use of relevant data. Our approach is different and is based on computationally inexpensive one-dimensional (partial differential equations) and zero-dimensional (algebraic and differential equations) models, see Devault et al. (2008). Two main challenges usually absent in hemodynamics are central here: (i) how to generate patient specific simulations and (ii) how to track and reduce uncertainties affecting the data, the model, the parameters and the geometry. The first question pertains to data assimilation and the second to uncertainty quantification.

2. DATA ANALYSIS

The acquired database includes 167 older adults (ages between 50 and 85 years old). A complete dataset for each subject includes: demographic data, laboratory values, TCD-based BFV during a 10 minute supine rest, CASL-based perfusion, blood pressure CO_2 at baseline, during hypercapnia and hypocapnia and cognitive challenge; anatomical high resolution T1-and T2-weighted MR imaging and time of flight, MR angiography (TOEF MRA) at 3 Tesla to characterize brain tissue volumes and the Circle of Willis (CoW) and plasma hematocrit. Subjects participated in the protocols approved by the Institutional Review Board at

the Beth Israel Deaconess Medical Center. The demographic characteristics are: 83 women, mean age 65.7 ± 8.4, 84 hypertensive, 83 normotensive, 62 diabetic. TCD waveform were reviewed and only good quality recordings were accepted for the analysis. We consider in the present study only measurements for the Middle Cerebral Artery (MCA).

2.1. Model and assumptions

The calculations from TCD measured BFV to CBF involves several assumptions. TCD measures Doppler shifts, see for instance Fodale et al (2007). More precisely, if f0 is the ultrasound frequency at the source (usually around 2MHz), elementary physics implies

$$\text{Doppler shift} = 2\, f0\, v/c \qquad (1)$$

where v is the apparent velocity the moving erythrocytes in the vessel under consideration and c is the speed of sound in soft tissues (usually taken as about 1540 m/s). If the angle of incidence is zero, i.e., if the source is perfectly lined up with the vessel then v is equal to the velocity of the red blood cells in the vessel. Otherwise, if θ is the angle between the probe and the vessel, i.e., the insonation angle, then

$$v = u \cos\theta \qquad (2)$$

where u is the actual velocity. The BFV is assumed to have the following profile

$$u(x,r,t) = (k+2)/k \;\; (1-(r/R(x,t)^k)\; U(x,t) \qquad (3)$$

where U(x,t) is the cross-sectional average of the velocity at point x along the vessel and time t, r is the distance from the axial line and R(x, t) is the radius of the vessel. The flow profile parameter k in the expression above is thus essentially unknown. It is usually assumed that k=2 which is the classic Poiseuille flow (parabolic profile); higher values of k correspond to flatter profiles.

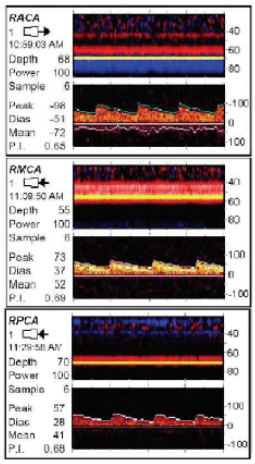

Figure 1: Typical TCD BFV results.

All erythrocytes do not travel at the same speed and the TCD analysis has the great advantage of gathering all spectral info corresponding to the flow, see Figure 1. However in most studies (including the present one) only the values corresponding to the upper envelope of the velocity are kept and averaged over time (leading to v).

Assuming the above profile, the average (in time) maximum (in space) velocity v can be used to express the overall average velocity as k/(k+2) v. Consequently, CBF values can be obtained from BFV data through

$$\text{CBF} = k/(k+2)\; \pi R^2\, v/(M \cos\theta) \qquad (4)$$

where M the MCA territory mass.

2.2. Lack of correlation across methods

Our results bring to the fore several surprising issues. There is no notable correlation between TCD BFV measurements and MRI (CASL) CBF measurements, as shown in Figure 2.

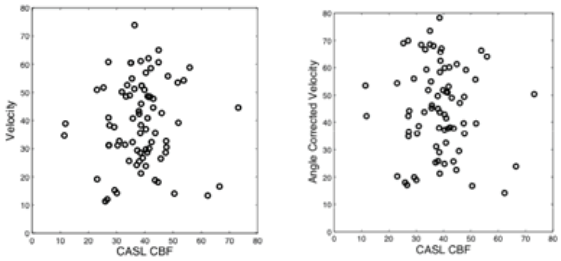

Figure 2: TCD BFV measurements vs. CASL CBF.

Remarkably, correlation does not notably increase if the TCD velocity measurements are corrected by the geometric factor (cosine) linked to the measured insonation angles, see Figure 2, right.
A direct comparison between CASL CBF and TCD CBF is presented in Figure 3.

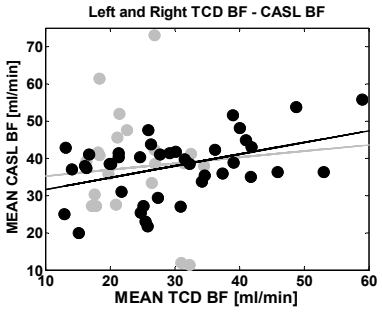

Figure 3: CBF measurement comparison

Correlations are again very low. Further analysis reveals that by splitting left and right side measurements and working only with high quality measurements, correlations between CASL CBF and TCD CBF are found in the .4-.5 range (with $p < .05$), see Figure 3.

Similar conclusions can be reached using Bland-Altman plots.

3. ANALYSIS OF THE SOURCES OF UNCERTAINTY

These low correlations stem from the following possible factors: (i) variability of the factors in the TCD CBF formula, (ii) variability in the TCD BFV measurements themselves, (iii) variability in the CASL CBF measurements. It is worth noting that comparisons of other types of methods lead to similar conclusions see for instance Bookers et al. (2010) for a comparison between ASL MRI and position emission tomography (PET), and systematic overestimating of CBF by ASL. We discuss these aspects below.

3.1. Insonation angle

The insonation angle is not available during routine TCD exam and thus often neglected. Based on 3D-TOEF images, that display both vessels and skull, and with approximate insonation site, these angles can be a posteriori estimated using elementary geometry and insonation depth. Figure 4 displays the values of insonation angle as a function of the measuring depth for a representative group of patients.

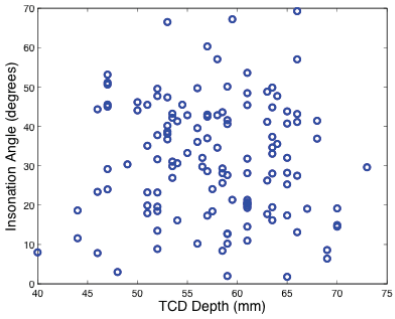

Figure 4: insonation angles vs. measurement depth

The insonation depth is chosen by the operator to optimize signal quality. Two conclusions can be drawn from Figure 4. First, there is no across patient correlation between insonation angle and measurement depth. Second, with an average insonation angle above 30 deg., the geometric factor linked to the insonation angle cannot be ignored.

3.2. Territory mass

The MCA territory mass M is the amount of brain tissue (in units of 100g) that is supplied blood by the two MCAs. The proportion of the brain corresponding to M is unknown and varies from person to person.

We assume the MCA territory mass to be between 35 and 50% of the total brain mass. For our calculations, we split the difference and consider the MCA territory to be 42.5% of the whole brain. Furthermore, we assume that both the left and right MCAs supply equal portions of the brain with blood, so that each artery is responsible for 21.25% of the blood supply to the brain.

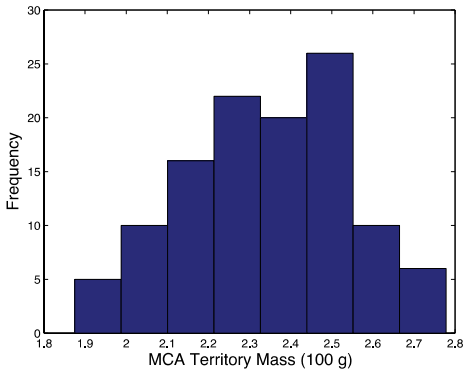

Figure 5: histogram of MCA territory mass

The histogram from Figure 5 suggests that the MCA territory mass roughly follows a normal distribution, with sample mean 2.34 and standard deviation 0.21.

3.3. Uncertainties in velocity data

The value of the velocity profile parameter k is unknown. The TCD protocol assumes that at all times the spatial maximum value of the velocity is obtained. For the assumed velocity profile, the standard deviation in the radial direction is found to be $U/\sqrt{k+1}$.

The measured value v is also assumed to be the temporal average of the velocity. This operation is typically carried internally through proprietary software from the manufacturer of the TCD apparatus. The resulting errors are therefore difficult to assess.

3.4. Resulting uncertainties in TCD CBF

The multiplicating factor to the velocity v in the TCD CBF formula, i.e, $k/(k+2)\ \pi R^2/(M\ \cos\theta)$, can be estimated. Based on the above assumptions, and for a profile factor k = 2, the corresponding distribution is displayed in Figure 6. This gives a first representation of the uncertainties attached to CBF predictions based on TCD.

The large spread of values is a clear indication that, in addition to the velocity data, supplementary patient specific information is needed to guarantee acceptable accuracy.

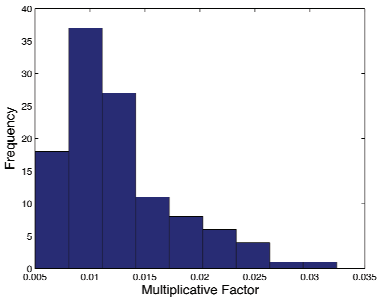

Figure 6: Statistical data for the multiplicative factor of the velocity v in the TCD CBF formula of Section 2.1 (mean is .0124).

3.5. Dependence on hematocrit

The CASL data are also subject to uncertainties.

Blood viscosity, clinically measured as hematocrit, affects not only red cell velocity but also tissue perfusion, labeled blood transfer into the tissue, and iron-induced T1 shortening of magnetization relaxation time (spin-lattice) (Silvoinnen et al., 2003).

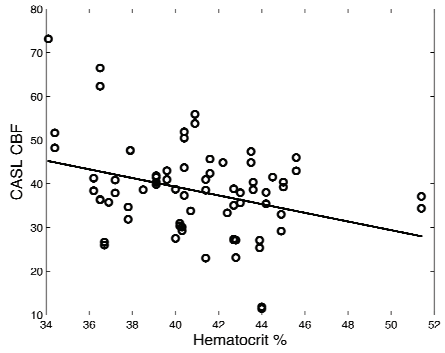

Figure 7: CASL CBF vs. hematocrit %, r = -0.33, p = 0.0034

As shown in Figure 7, hematocrit is strongly and negatively correlated with CASL estimates and therefore people with lower hematocrit may have higher perfusion estimates. This factor may account for example for gender differences in perfusion and over-estimate perfusion in the elderly (Zhao et al., 2009). The longer transit time, as seen with low perfusion states e.g. hypocapnia or small vessel disease in aging, may in contrast lower perfusion estimates, and contribute to differences among vascular territories due to the short decay time of the CASL label (~1s). Therefore, post-labeling delay in conjunction with hematocrit effects may induce under - and over estimation of perfusion values (Thomas 2009).

CASL, fMRI-derived hemodynamics were concordant with $H_2{}^{15}O$ PET, which is considered a gold standard for CBF imaging (Carroll, et al., 2002),

4. CONCLUSION

TCD and CASL CBF values are only weakly correlated. This is explained by the range of uncertainties attached to parameters entering both protocols: vessel radii, territory mass, insonation angle, velocity profile for TCD and perfusion territory and hematocrit dependence for CASL. Some of the TCD uncertainties can be mitigated. For instance, the analysis of the full spectral information rather than just the envelope may give information about the velocity profile; likewise, insonation angles can be estimated for each patient.

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