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An Extended Model of Intracranial Latency Facilitates Non-Invasive Detection of Cerebrovascular Changes

Shadnaz Asgari¹, Andrew W. Subudhi^{4,5}, Robert C. Roach⁵, David S. Liebeskind³, Marvin Bergsneider^{1,2}, and Xiao Hu^{1,2}

¹ Neural Systems and Dynamics Laboratory, Department of Neurosurgery, David Geffen School of Medicine, University of California, Los Angeles

² Biomedical Engineering Graduate Program, Henry Samueli School of Engineering and Applied Science, University of California, Los Angeles

³ Stroke Center, Department of Neurology, David Geffen School of Medicine, University of California, Los Angeles

⁴ Department of Biology, University of Colorado at Colorado Springs, Colorado Springs, Colorado

⁵ Altitude Research Center, School of Medicine, University of Colorado at Denver, Denver, Colorado

Abstract

A method has been recently developed to reduce the confounding factors of extracranial origins on the intracranial latency (the time interval between the electrocardiogram QRS component and the initial inflection of the resulting pulse). Although, the proposed model was shown to portray a better characterization of cerebral vasculature, the parameters of the model and their physiological interpretations have not been fully explored. The present work improves the physiological understanding of these parameters, refines the model and extends its ability to monitor real-time changes in overall cerebrovascular resistance. We show that the slope of the linear model which relates the latency of arterial blood pressure to that of the cerebral blood flow velocity, could be a measure of resistance, and that the intercept is a function of slope and pre-ejection period. A dataset of cerebral blood flow velocity and arterial blood pressure signals from 18 normal subjects at rest was used to validate the derived parameters of the model. Also, the results of further data processing verified our hypothesis that the slope of the model would significantly increase during a period of CO₂ rebreathing, due to dilation of the vessels and reduction of cerebrovascular resistance ($p \leq 0.02$). Finally as the slope of the proposed model is shown to be highly correlated with other conventional measures of cerebrovascular resistance, (resistance area product and critical closing pressure), we conclude that the derived slope metric is a measure of overall cerebrovascular resistance and therefore could be useful in guiding the non-invasive cerebrovascular management of patients.

Keywords

cerebral blood flow; cerebrovascular status; cerebrovascular resistance; intracranial latency; pulse wave velocity

Corresponding Author: Xiao Hu, Ph.D., 18-265 Semel, Box 703919, 10833 Le Conte Avenue, Los Angeles, CA 90095, Office: (310) 206-3416, FAX: (310) 983-1089, xhu@mednet.ucla.edu.

7-Disclosure/Conflict of Interest

The authors do not have any conflict of interests.

1-Introduction

Management of several neurological conditions (e.g. traumatic brain injury and subarachnoid hemorrhage) requires information related to the structural and functional changes of the cerebrovascular system. For instance, pathological narrowing of cerebral arteries (vasospasm) that follows aneurysmal or traumatic subarachnoid hemorrhage, if not treated in a timely manner, can lead to cerebral ischemia (Harrod et al., 2005; Mayberg et al., 1994). Due to practical limitations imposed by the skull, real-time and continuous assessment of intracranial vasculature states, such as arterial vasoconstriction or autoregulatory capacity, is a clinically challenging task.

One solution to this problem could be utilizing the pulse wave velocity (PWV) analysis, analogous to work previously employed for the effective assessment of the state of systemic vasculature; e.g. calculation of vessel elasticity, impedance and reflection coefficients (Nichols and O’rourke, 2005), and arterial stiffness index (Chang et al., 2006). The underlying principle is based on the Moen-Korteweg equation which describes PWV as a function of basic properties of the vascular route, such as internal radius and wall thickness of the vessel (Nichols and O’rourke, 2005).

To our knowledge, Giller and Aaslid were first to apply a PWV approach to the analysis of the intracranial arterial system (Giller and Aaslid, 1994). They specifically calculated the PWV in the peripheral circulation using the measurements of time delays between cerebral blood flow velocity (CBFV) waveforms obtained simultaneously from the cervical carotid artery and the ipsilateral middle cerebral artery (MCA). Since then, there have been limited studies for the assessment of cerebral vasculature using PWV (Alastruey et al., 2007; Gladdish et al., 2005; Perez et al., 2005). The lack of studies is partially due to the difficulty of direct measurement of cerebral PWV imposed by the bony skull. As a result, employing an indirect measure of PWV (e.g. intracranial pressure (ICP) pulse latency or CBFV pulse latency) could be potentially helpful. By defining pulse onset latency as the time interval between the QRS component and the initial inflection of the resulting pulse, one can conclude that changes in pulse latency reflect pathophysiological changes of the cerebral vasculature (Hu et al., 2008). Although, timing pulse onset relative to electrocardiogram QRS is practical, it introduces confounding factors of extracranial origins. This is due to the fact that the physiologic changes occurring anywhere from the cardiac sinus node to the skull base could confound the ability to infer intracranial changes.

Our group recently developed a method to reduce these confounding influences by modeling the relationship between CBFV latency and systemic arterial blood pressure (ABP) pulse latency (Hu et al., 2009). Although the results of the former work showed that the proposed CBFV latency correction approach produced a more accurate measure of cerebrovascular changes, it did not fully explore the parameters of the proposed model and their physiological interpretation. The physiological interpretation of the parameters of the model could provide us with deeper insight into the model and its further potential in the characterization of the cerebrovascular status. Moreover, in the previous work, the model was only validated on a dataset of subjects undergoing pressure cuff test which only causes short-lasting cerebral vascular changes.

The objectives of the present work are two fold: 1) To validate the model parameters and explain their physiological significance; and 2) To test the model using a unique data set in which subjects rebreathed CO₂ to elicit a progressive degree of cerebral vasodilation. Therefore, we refine the former model so as to reveal intracranial latency as a linear function of systemic latency where the slope is a measure of cerebrovascular resistance. We also

demonstrate that the intercept of the model is itself a function of slope and pre-ejection period (PEP). Validation of the model is performed by showing its ability to qualitatively replicate Weissler's relationship between PEP values and heart rate (Weissler et al., 1968) using a dataset of CBFV and ABP signals from 18 normal subjects. In order to test the adequacy of the proposed model for the non-invasive monitoring of real-time changes in overall cerebrovascular resistance, we hypothesized that CO₂ rebreathing would dilate vessels and lead to a longer intracranial latency compared to eucapnic breathing. So based on the proposed mathematical model, an increase in the value of slope would be expected during the CO₂ rebreathing state. Finally, we compare the derived slope metric with two other existing measures of cerebrovascular resistance, resistance area product and critical closing pressure (Payne et al., 2006), and demonstrate that our derived slope metric is highly correlated with these measures.

2-Materials and Methods

2-1- A Review on the Latency Modeling of Arterial Blood Pressure and Cerebral Blood Flow Velocity Pulses

A schematic representation of the components of ABP latency (LT_{ABP}) and CBFV latency (LT_{CBFV}) has been illustrated in figure 1, where LT_{Shared} (a shared latency component that is common to both the ABP and CBFV waveforms) represents the time interval from the QRS components of electrocardiograph (ECG) to the time when blood pressure pulse reaches the juncture point between the extra- and intracranial components. LT_{Radial} and LT_{MCA} represent the traveling time of blood pressure pulse from the terminal point of the LT_{Shared} to the radial artery assessment and to the CBFV measurement point, respectively.

As a result, we have the following equation,

$$\begin{aligned} LT_{ABP} &= LT_{Shared} + LT_{Radial}, \\ LT_{CBFV} &= LT_{Shared} + LT_{MCA}. \end{aligned} \quad \text{eq.(1)}$$

Given the fact that flow velocity pulse usually leads pressure pulse (Nichols and O'rourke, 2005), LT_{CBFV} includes the intrinsic negative value phase difference between pressure and flow velocity pulse measured at the same site. Note that LT_{Radial} and LT_{Shared} are related to the pulse wave velocities of their representative vascular segments (v_{Radial} and v_{Shared}) based on the following equations,

$$\begin{aligned} LT_{Shared} &= PEP + \frac{D_{Shared}}{v_{Shared}}, \quad (a) \\ LT_{Radial} &= \frac{D_{Radial}}{v_{Radial}}, \quad (b) \end{aligned} \quad \text{eq.(2)}$$

where PEP is the cardiac pre-ejection period (the period between the ventricular contraction and the opening of semilunar valves and blood ejection into the aorta), and D_{Shared} and D_{Radial} are lengths of the vascular segments from the heart to the origin of the juncture node and from this juncture node to the location of measurement of ABP on the radial artery, respectively. By defining α as the constant ratio of pulse wave velocities at these two vascular segments ($\frac{v_{Radial}}{v_{Shared}}$), it can be shown that

$$\begin{aligned}
 LT_{Radial} &= K_1 \times LT_{Shared} - K_0, \\
 K_0 &= \frac{D_{Radial} \times PEP}{D_{Shared} \times \alpha} = K_1 \times PEP, \\
 K_1 &= \frac{D_{Radial}}{D_{Shared} \times \alpha}.
 \end{aligned}
 \tag{eq.(3)}$$

Following some mathematical derivations, LT_{CBFV} can be expressed in terms of LT_{ABP} with the following equation

$$LT_{CBFV} = \frac{LT_{ABP}}{1+K_1} + \frac{K_0}{1+K_1} + LT_{MCA}.
 \tag{eq.(4)}$$

Now, a corrected beat-by-beat CBFV latency ($cLT_{CBFV}(i)$, $i = 1, \dots$) can be obtained by implementing a subtraction procedure where scaled systemic pulse latency and a constant term were extracted from the measured $LT_{CBFV}(i)$,

$$cLT_{CBFV}(i) = LT_{CBFV}(i) - \left(\frac{K_0 + LT_{ABP}(i)}{1+K_1} + \overline{LT_{MCA}} \right),
 \tag{eq.(5)}$$

$\overline{LT_{MCA}}$ is a component of LT_{MCA} that does not change from sample to sample. This corrected CBFV latency represents the information more directly related to the sample-to-sample changes in the cerebrovasculature by essentially removing the extracranial confounding influence and consequently improving the positive correlation between CBFV and the CBFV latency time series. For more details on this model and its validation process, the readers are referred to (Hu et al., 2009).

2-2- Extension of the Existing Model in order to Interpret Slope and Intercept as Cardio-Cerebrovascular Metrics

The aforementioned model has been shown to reduce the influence of confounding factors of extracranial origins for characterizing the cerebral vasculature. This impels us to further investigate the physiological interpretation of the parameters of the model. But since the slope and intercept of the linear model in its present form are not the optimally condensed expression of the CBFV latency in terms of ABP latency, we need to modify the model by expressing LT_{MCA} as

$$LT_{MCA} = \frac{D_{MCA}}{v_{MCA}} = \frac{D_{MCA}}{\beta \times v_{Shared}},
 \tag{eq.(6)}$$

where D_{MCA} and v_{MCA} are the lengths and pulse wave velocities of the vascular segments from the juncture node to the location of measurement of CBFV on the MCA, respectively. β is the constant ratio of pulse wave velocity at the aforementioned segment to the pulse wave velocity of the vascular segment from the heart to the origin of the juncture node ($\frac{v_{MCA}}{v_{Shared}}$). Substituting the equivalent of v_{Shared} from equation (2-a) in equations (6) led to

$$LT_{MCA} = K_2 \times (LT_{shared} - PEP),$$

$$K_2 = \frac{D_{MCA}}{\beta \times D_{Shared}}.$$
eq.(7)

Since $LT_{ABP} = LT_{Radial} + LT_{shared}$, combining equations (3-a) and (7) resulted in

$$LT_{MCA} = K_2 \times \frac{K_0 + LT_{ABP}}{1 + K_1} - K_2 \times PEP.$$
eq.(8)

Now, by merging equations (4) and (8), we will have the following equation

$$LT_{CBFV} = \frac{1 + K_2}{1 + K_1} LT_{ABP} + \frac{K_1 - K_2}{1 + K_1} PEP,$$
eq.(9)

which can be rewritten as the following linear equation

$$LT_{CBFV}(i) = Slope \times LT_{ABP}(i) + Intercept,$$
eq.(10)

where

$$Slope = \frac{1 + K_2}{1 + K_1} = \frac{1 + \frac{D_{MCA}}{\beta \times D_{Shared}}}{1 + \frac{D_{Radial}}{\alpha \times D_{Shared}}},$$

$$Intercept = \frac{K_1 - K_2}{1 + K_1} \times PEP,$$
eq.(11)

and $LT_{ABP}(i)$ and $LT_{CBFV}(i)$ are ABP and CBFV latencies of the i^{th} beat ($i = 1, 2, \dots, N$) in the data segment. The derivation for the *Intercept* can be further simplified as

$$Intercept = \frac{K_1 - K_2}{1 + K_1} \times PEP = \frac{1 + K_1 - (1 + K_2)}{1 + K_1} \times PEP = \left(1 - \frac{1 + K_2}{1 + K_1}\right) \times PEP,$$
eq.(12)

Now replacing the equivalent of *Slope* from equation (11) to equation (12) will result in

$$Intercept = (1 - Slope) \times PEP = -PEP \times Slope + PEP.$$
eq.(13)

The extended latency model of equations (10), (11) and (13) indicates the following interesting remarks which were not apparent in the original model of (Hu et al., 2009).

1. *Intercept* is itself a function of *Slope* and *PEP*. In a segment of data with a short time duration, since the value of *PEP* does not change substantially (Payne et al., 2006), *Intercept* would be a linear function of *Slope*.

2. Since D_{MCA} , D_{Radial} and D_{shared} are constant in an individual patient, *Slope* could be useful in detecting relative cerebrovascular changes because it is a function of pulse wave velocities of the cerebral vasculature and the upper-limb vasculature. Particularly, it can be concluded that pulse wave velocity, and hence blood vessel stiffness and vascular resistance in the cerebral vasculature, would be negatively correlated with the slope. For example, a selective vasodilation of cerebral arteries would decrease cerebrovascular resistance and PWV in the related cerebral vasculature and result in, based on equation (10), an increase in the value of slope. Note that this analysis provides a measure to capture the static property of the cerebral vasculature while the previous methodology (Hu et al., 2009) to estimate $LT_{CBFV}(i)$ (equation (5)), provided means to capture the dynamic changes. However, extracting *Slope* using consecutive segments of data would enable a continuous surveillance of the cerebral vasculature using continuous ABP, CBFV, and ECG measurements.
3. Using the extended model of equations (10) and (13), one can estimate the average value of PEP ($\overline{PEP}$) over a specific time duration. This can be achieved by implementing the following procedure; the beat by beat estimated ABP and CBFV latency data will be divided to consecutive overlapping data segments where each segment has a short time duration (consisting of N beats). If we use index j , $j \in \{1, 2, \dots\}$ to indicate the j^{th} of such a segment, then the $Slope(j)$ and $Intercept(j)$ for that segment can be calculated using equation (10). Now let us define $\mathbf{S} = \begin{bmatrix} Slope(1) & Slope(2) & \dots & Slope(j) & \dots \end{bmatrix}^T$, and $\mathbf{I} = \begin{bmatrix} Intercept(1) & Intercept(2) & \dots & Intercept(j) & \dots \end{bmatrix}^T$. A linear regression model could then be applied to the vectors of calculated slopes ($\mathbf{S}$) and intercepts ($\mathbf{I}$) as $\mathbf{I} = \gamma \times \mathbf{S} + \delta$. Now based on equation (13), the average pre-ejection period would be equal to the slope of the obtained regression model with the negative sign. In other words, $\overline{PEP} = -\gamma$.

In the next section, we will describe the dataset which has been used in this paper to test whether data during re-breathing test will support the above points.

2-3- Testing the Model

We tested the hypothesis that the refined latency model would be sensitive to changes in cerebral resistance, where increased pial vessel diameter induced by CO_2 rebreathing, would reduce cerebral resistance, increase LT_{MCA} and thus result in a steeper slope metric.

2-3-1- Subject Data—Data were obtained from a portion of a larger study investigating cerebral hemodynamics during exposure to hypobaric hypoxia conducted at the University of Colorado Denver, Anschutz Medical Campus, as previously described in (Subudhi et al., 2010). Briefly, 28 healthy, consenting individuals were instrumented to monitor partial pressure of end-tidal carbon dioxide (PETCO_2) (Ametek CD-3A, AEI Technologies, Pittsburgh, PA USA), ECG (Bioamp, ADInstruments, Colorado Springs, CO USA) and beat-by-beat changes in radial artery blood pressure (Model 7000, Colin Medical Instruments, San Antonio, TX USA) and ipsilateral MCA flow velocity (Multi-Dop T2, DWL Electronic Systems, Singen, Germany). Signals were synchronized and recorded simultaneously at a sampling rate of 400 Hz (Powerlab 16SP, ADInstruments, Colorado Springs, CO, USA). Data was collected in the supine position, to avoid hydrostatic differences in arterial pressure. After 6 min of rest, subjects underwent a series of tests in which fractional concentrations of inspired gases and breathing rate were manipulated to evaluate baseline, normoxic cerebral hemodynamic parameters, including cerebral autoregulation and

vasomotor reactivity. Between tests, partial pressure of end-tidal oxygen (PETO₂) returned to baseline values established at rest. During the CO₂ rebreathing segment used in the present study, subjects were asked to take 2 to 3 deep breaths of 7.5% CO₂, 60% O₂, balance N₂, then rebreath through ~15-L circuit until PETCO₂ rose to above 50 mmHg.

After inspection for data quality, it was determined that 10 subjects had insufficient ECG signals (intermittent cable shortage) during either the resting or CO₂ rebreathing tests. Since in the proposed model, the latencies of the CBFV and ABP are defined with respect to electrocardiogram QRS complex, the subjects with poor ECG signals were excluded from the further study. This exclusion resulted in processing of the data from remaining 18 subjects (11 males and 7 females; 18 to 38 years). The mean duration of the resting and CO₂ rebreathing tests for these subjects were 5.77 ± 0.86 min and 4.28 ± 1.04 min, respectively.

ECG QRS detection was performed using a previously published algorithm (Afonso et al., 1999) on lead II of the ECG. Then, an ECG-aided pulse detection algorithm (Hu et al., 2008) was used to delineate each pulse of ABP, CBFV and PETCO₂. In addition, each detected ABP and CBFV pulse was saved and visualized using the custom software developed in-house to screen obvious noise or artifacts, so that only clean beats were further processed. Then the following beat-by-beat parameters were derived for the beats of ABP and CBFV that passed the screen test mentioned above; ABP latency (LT_{ABP}), CBFV latency (LT_{CBFV}), mean ABP ($\langle ABP \rangle$), mean CBFV ($\langle CBFV \rangle$), mean PETCO₂ ($\langle PETCO_2 \rangle$) and heart rate ($HR = \frac{60}{R-R \text{ Interval}}$). Latencies were measured from the onset of each pulse relative to ECG QRS. The onset was automatically located using the tangent intersect method (Chiu et al., 1991).

2-3-2- Model Validation—Consecutive data segments of $N=20$ beats with 95% overlapping were used to calculate vectors of slope (**S**) and intercept (**I**) and obtain the average pre-ejection period $\overline{PEP}$ for each subject, as described in section 2.2. In addition, the following three parameters were calculated for the fitted linear regression model to vectors of **S** and **I**; R-square statistic (R^2), probability value for the full model (p), and sample standard deviation from regression model in ms (SD).

The current clinical gold standard method for assessing pre-ejection period is echocardiography (Cokkinos et al., 1976; Hirschfeld et al., 1975), but since echocardiograms were not included in the mountain sickness study design, the accuracy of the estimated $\overline{PEP}$ was assessed by comparing the results with those obtained from another method of indirect measurement of $\overline{PEP}$ known as Weissler method (Weissler et al., 1968). Weissler et al. relate the average pre-ejection period of a normal individual to the average heart rate ($\overline{HR}$) with the following equation

$$\overline{PEP} = -0.4 \times \overline{HR} + 131, \quad \text{eq.(14)}$$

where $\overline{PEP}$ is expressed in ms and $\overline{HR}$ is in (beats/min).

2-3-3- Comparison of Computed Slope Metric during CO₂ rebreathing and Resting State—Since the time lengths of both resting and CO₂ rebreathing tests were different from subject to subject, the following procedure was implemented to obtain the group averaged values of slope and intercept over time. For each subject a data segment of 40 beats with 95% overlapping was used to calculate the slope and intercept over the last T_{Rest} seconds of rest and the first T_{Rebreath} seconds of rebreath where T_{Rest} and T_{Rebreath} are

the minimum time lengths of the resting and CO₂ rebreathing tests over all subjects, respectively.

2-3-4- Comparison of the Computed Slope Metric with Other Conventional Measures of Cerebrovascular Resistance—We used the FFT-based method to calculate two of the existing measures of cerebrovascular resistance; critical closing pressure (CCP) and resistance area product (RAP) (Panerai, 2003) during both resting and CO₂ rebreathing states. Then a correlation analysis between each of these measures and the proposed slope metric has been performed.

3-Results

3-1- Model Derivation/Description

Figure 2 shows the plots of ABP, estimated ABP latency, CBFV, estimated CBFV latency, heart rate, estimated slope vector (**S**) and estimated intercept vector (**I**) (obtained from equation (10)) and their one-to-one relationship for one subject at rest. Each point on any of these plots is obtained by applying a moving average window of 20 beats with 95% overlapping on the beat-to-beat time series of the corresponding physiological parameter.

We observe that all the depicted parameters are stable over time; as is expected at rest, and the estimated values of CBFV latency (with mean of 135.43 ms) are smaller than those of ABP latency (with mean of 193.68 ms). As figures 2-f and 2-h show, estimated slope (with mean of 1.03) is always a positive number, while intercept (with mean of -64.30) has a negative value most of the time. Please note that, disregarding the scaling of the y-axis, the plots of estimated slope and intercept over time are mirror image of each other relative to the x-axis. Figure 2-g demonstrates the estimated intercept values versus their corresponding slope and also a line that has been fitted to these points as $Intercept = -196.7 \times Slope + 138.5$. The three formerly described parameters for this fitted line are as the following: ($R^2 = 0.99$), ($p \leq 10^{-3}$) and ($SD = 1.15$). In fact, the mean and standard deviation of these three parameters over all 18 subjects are ($R^2 = 0.99 \pm 0.01$), ($p \leq 10^{-3}$) and ($SD = 1.47 \pm 0.45$). These numbers show that the estimated *Slope* and *Intercept* are linearly related.

Figure 3 demonstrates the estimated values of $\overline{PEP}$ calculated following the procedure described in section 2.2. and compares those with the estimated values from Weissler model of equation (14).

We observe that although the estimated pre-ejection values from the proposed latency model and Weissler equation do consistently depict different estimation biases (the mean difference between estimated $\overline{PEP}$ values of both methods is 101.67 ± 12.74 ms), they correlate to a modest degree (correlation coefficient of 0.67 and R-squared value of 0.45) and follow the same changes. As a result, the estimated $\overline{PEP}$ values from the proposed model could be a good qualitative measure of $\overline{PEP}$ values obtained from Weissler equation.

3-2- Comparison of Computed Slope Metric during CO₂ rebreathing and Resting State

Figure 4 shows the plots of ABP, estimated ABP latency, CBFV, estimated CBFV latency, heart rate, estimated slope vector (**S**), estimated intercept vector (**I**) and PETCO₂ when the subject of figure 2 undergoes the CO₂ rebreathing test.

Each point on these plots is obtained by applying a moving average window of 20 beats with 95% overlapping on the beat-to-beat time series of the corresponding physiological parameter. Please note that the time length of the CO₂ rebreathing experiment (which was set based on the level of subject's tolerance) and the starting/ending level of PETCO₂ are

different from subject to subject, but the following phenomena were observed for all the subjects during the CO₂ rebreathing test; as the subject rebreathed, the level of PETCO₂ and consequently CBFV increases over time, whereas the ABP signal does not either change significantly or increases slightly comparing to that of CBFV (Vantanajal et al., 2007). Heart rate usually decreases first, but then starts to recover and finally stabilizes at a rate that is different from subject to subject. We also observe that CBFV latency and ABP latency are highly correlated at the beginning of the CO₂ rebreathing test (both increase).

Figure 5 shows the mean and standard deviation of the estimated slope and intercept calculated over all 18 subjects during the last $T_{\text{Rest}}=190$ seconds of rest and the first $T_{\text{Rebreath}}=100$ seconds of CO₂ rebreathing, respectively.

We observe that during the CO₂ rebreathing test the slope increases while the intercept decreases, reflecting the reduction in cerebrovascular resistance. The mean of slope during rest and CO₂ rebreathing are 0.99 and 1.12 respectively, whereas the mean of intercept during rest and CO₂ rebreathing are -67.50 and -94.10 respectively. Also a t-test on the increase of slope and decrease of intercept when the subject goes from the resting test to CO₂ rebreathing test results in $p=0.006$ and $p=0.011$, respectively. This indicates that the value of slope significantly increases and the value of intercept significantly decreases, when the subjects at resting begin to rebreath CO₂.

3-3-Comparison of the Computed Slope Metric with Other Conventional Measures of Cerebrovascular Resistance

Figure 6 compares the average slope metric calculated over all 18 subjects with two of existing measures of cerebrovascular resistance (RAP and CCP) during the resting and CO₂ rebreathing. We observe that all the three aforementioned parameters are relatively constant during the resting, but as the subjects start to rebreath CO₂, slope increases while the other two measures of cerebrovascular resistance demonstrate a decreasing pattern. A simple correlation analysis indicates that the slope metric is highly correlated with RAP and CCP with correlation coefficients of -0.89 and -0.89, respectively.

Table 1 displays the mean and standard deviation of all the related parameters calculated over all subjects during resting and CO₂ rebreathing and highlights the ones which are significantly different between resting and CO₂ rebreathing; CBFV and CBFV latency, slope and intercept of the proposed model, RAP and CCP

4- Discussion

Applying algorithms motivated from employment of pulse wave propagation to characterize the cerebral vasculature have been shown to be feasible by our previous (Hu et al., 2009) and current work. Although studies of such algorithms in the cerebrovascular context only appeared recently (Alastruey et al., 2007)(Perez et al., 2005), much success has been achieved in the context of characterizing systematic circulatory bed. Due to the limitation of measurement techniques, one particular aspect for the cerebrovascular applications is to deal with the confounding influences of extracranial origins on any metric intended for characterizing the cerebrovascular changes exclusively. This was addressed in our previous work by using a simple model of the relationship between intracranial and extracranial latency.

The main contribution of the present work is the evaluation of the physiological importance of the parameters of the previous model and demonstrating the intrinsic relationship between the slope and intercept parameters of the model. As the slope metric is shown to be highly correlated with two other conventional measures of the cerebrovascular resistance, the

potential of the proposed model was established beyond reduction of the confounding factors of the extra-cranial origins on the intracranial latency. Moreover, the present work was able to validate the previous model on a different set of data where the subjects undergo CO₂ rebreathing test which introduces cerebral vascular changes of longer duration than that of cuff-test used in our previous work.

4-1-Model Validation

The fact that the plots of estimated slope and intercept over time are mirror image of each other demonstrates that the two parameters must be linearly related. Note that, based on equation (13), it was already expected for the estimated slope and intercept to be linearly related. But the former equation also indicates that the line plot of *Intercept* versus *Slope* should have a slope equal to $-PEP$ and must intersect the y-axis at the value equal to PEP . However, this is not consistent with the fitted line of figure 2-g as $Intercept = -196.7 \times Slope + 138.5$. This is related to the fact that flow velocity pulse usually leads pressure pulse (Nichols and O’rourke, 2005) and consequently LT_{CBFV} includes the intrinsic negative value phase difference between pressure and flow velocity pulse measured at the same site. In other words, considering this phase difference (τ), one can correct equation (13) to relate *Intercept* and *Slope* as the following

$$Intercept = (1 - Slope) \times PEP - \tau, \quad \text{eq.(15)}$$

This correction could further justify the mostly negative values of estimated intercept in figure 2-h even when the estimated slope is smaller than one. Given this reasoning, we can then focus on investigating the quality of the PEP estimate to validate the proposed model. This is a challenging task given that no direct measurement of PEP is available for this dataset. We therefore resorted to using an empirical but widely accepted PEP estimation method (Weissler et al., 1968) that is based on the heart rate. Similar to Weissler’s estimate, the *PEP* values from our model are negatively correlated with the heart rate and follow the same changes as the Weissler estimate (figure 3-b). We also noted that the absolute values of the two PEP estimates do not match. However, this could be attributed to the ambiguity of the definition of PEP in Weissler model where PEP was defined as the interval from QRS complex to the beginning of the upstroke of the carotid arterial pulse. But the “beginning of the upstroke” has been never accurately described, which is likely to be different from the definition used by us (the interval from QRS complex to the characteristic point of the employed tangent latency estimation (Chiu et al., 1991) on the pressure pulse).

Please note that although *PEP* may be estimated as a by-product of the proposed model, *PEP* estimation analysis in this paper has been just employed to validate the model and as a result, its clinical significance and implication are not the focus of the present work.

4-2-Comparison of Computed Slope Metric during CO₂ Rebreathing and Resting State

The CO₂ rebreathing test is a cerebral vasomotor reactivity test, where a steeper slope between MCA velocity and PETCO₂ indicates greater vessel reactivity. Figures 4-f and 4-h show that the estimated value of slope increases when the subjects enter CO₂ rebreathing state. CO₂ rebreathing introduces vasodilation causing a decrease in cerebral pulse wave

velocity (v_{MCA}) and hence a decrease in the value of $\beta = \frac{v_{MCA}}{v_{Shared}}$. Because $Slope = \frac{1 + \frac{D_{MCA}}{\beta \times D_{Shared}}}{1 + \frac{D_{Radial}}{\alpha \times D_{Shared}}}$, if β decreases, then slope would increase. Now one may argue about the possibility of a decrease in α as a result of a possible decrease in v_{Radial} during the CO₂ rebreathing test.

Please note that hypercapnia during re-breathing test is expected to have more pronounced vasodilation influence on the cerebral vasculature than the systemic arterial bed. So even if we assume both α and β decrease as CO_2 level rises, one can expect for a larger decrease of β compared to that of α . In addition, D_{MCA} (the length of the vascular segment from the juncture node to the location of measurement of CBFV on the middle cerebral artery) is almost less than 30% of the D_{Radial} (length of the vascular segments from the juncture node to the location of measurement of ABP on the radial artery) (Giller and Aaslid, 1994; Nichols and O'rourke, 2005). So it is expected that the slope increases during CO_2 rebreathing test, as long as the decrease in β is greater than only 30% of the decrease in the parameter α , which is evidently the case.

4-3-Comparison of the Computed Slope Metric with Other Conventional Measures of Cerebrovascular Resistance

Correlation between *Slope* and two existing metrics of cerebrovascular tone including RAP and CCP, has been shown to be significant (correlation coefficient = -0.89 , $p \leq 10^{-3}$). A negative correlation between *Slope* and these two metrics is also expected. As we discussed in the previous sub-section, *Slope* increases with cerebral vasodilation. On the other hand, CCP and RAP are expected to decrease with cerebral vasodilation, because vasodilation loosens cerebrovascular tone. Therefore, the correct polarity of correlation and a significant correlation value indicate that *Slope* metric is a valid measure in characterizing cerebrovascular tone and resistance. It should be noted that *Slope* and RAP/CCP are based on completely different theories. This also suggests that pulse wave propagation theory is a valid alternative theoretical foundation that can be leveraged for future studies of cerebral vasculature.

4-4- Implication for Continuous Monitoring of the Cerebral Vasculature

Since many of the same principles in terms of latency detection, analysis, and interpretation are fundamentally applicable to both intracranial pressure (ICP) and CBFV pulse waves, the *Slope* metric could also be calculated by using ICP pulse latency instead of CBFV pulse latency. The continuous acquirement of ICP pulse in the intensive care unit (relative to sporadic measurement of CBFV signal) would then enable the continuous assessment of the cerebral vasculature. Such a capability will be helpful in detection of several physiological events causing the cerebral vasculature changes relative to that of the systematic arterial bed, e.g. cerebral vasospasm which happens after aneurysmal subarachnoid hemorrhage (Gonzalez et al., 2007).

5- Conclusions

We refined a recently developed intracranial latency analysis model which was originally intended for better characterization of the cerebral vasculature. The new derivation provides a physiological interpretation of the parameters of the former model. Specifically, we showed that the slope of the model is a function of pulse wave velocities in the cerebral vasculature and in the upper-limb vasculature and could be used as a measure of cerebrovascular resistance, while intercept of the model represents a linear function of slope and pre-ejection period. The derivation of the parameters of the model was validated by qualitatively replicating the relationship between PEP and heart rate. We also demonstrated that the estimated slope increases (intercept decreases), after the subjects started CO_2 rebreathing and this observation is in agreement with the physiological underpinnings of the slope as revealed by the mathematical modeling of ABP and CBFV pulse latency. Finally, a correlation analysis between the slope of the proposed model and the resistance area product and critical closing pressure reveals that the proposed slope metric is a reliable measure of

cerebrovascular resistance and could be employed to successfully track the cerebral vasculature changes relative to that of the systematic arterial bed.

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10-Reference

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Figure 1. Schematic plot of the components of two latency benchmarks. LT_{ABP} is arterial blood pressure latency and LT_{CBFV} is cerebral blood flow velocity latency. Latencies are measured from the onset of pulse to the QRS peak of ECG.

Figure 2.

Plots of different signals extracted during the resting state of a subject. (a) ABP, (b) estimated ABP latency, (c) CBFV, (d) estimated CBFV latency, (e) heart rate, (f) estimated slope vector $\mathbf{S}$ and (h) estimated intercept vector $\mathbf{I}$ of a subject. Plot (g) depicts the linear relationship between estimated $\mathbf{I}$ and estimated $\mathbf{S}$. Signals are obtained using a moving average window of 20 beats with 90% overlapping

Figure 3.

Comparison of the estimated pre-ejection period obtained from the proposed model and the estimated $\overline{PEP}$ from Weissler regression model. (a) estimated pre-ejection period versus heart rate (b) estimated pre-ejection period for all the subjects at resting (c) scatter plot of estimated pre-ejection period using proposed method against that of the Weissler method. Please note that the two different scaling on the y-axis of the plots (a) and (b) are intended to magnify the changes in the estimated $\overline{PEP}$ from Weissler regression model.

Figure 4.

Plots of different signals extracted during the CO₂ rebreathing of a subject. (a) ABP, (b) estimated ABP latency, (c) CBFV, (d) estimated CBFV latency, (e) heart rate, (f) estimated slope vector, (g) PETCO₂ and (h) estimated intercept vector **I**. Signals are obtained using a moving average window of 20 beats with 90% overlapping

Figure 5.

Mean and standard deviation of the extracted parameters of the model over 18 subjects. (a) estimated slope, and (b) estimated intercept. The group averaged values are calculated for the last 140 seconds of resting and the first 95 seconds of CO₂ rebreathing, respectively. The slope increase (intercept decrease) during CO₂ rebreathing relative to the resting was statistically significant ($p \leq 0.02$).

Figure 6.

Comparison of the derived slope metric with some existing measures of cerebrovascular resistance. (a) derived slope, (b) resistance area product (RAP), and (c) critical closing pressure (CAP).

Table 1

Mean and standard deviation of all the parameters during resting and rebreathing states.

	Resting	CO ₂ rebreathing
ABP (mmHg)	84.91 ± 12.18	80.42 ± 780
ABP latency (ms)	208.80 ± 14.41	211.43 ± 14.10
CBFV (cm/s)	58.94 ± 12.59	76.82 ± 17.03*
CBFV latency (ms)	142.66 ± 14.26	148.94 ± 13.89*
Heart Rate (beat/min)	61.08 ± 9.15	60.66 ± 7.82
Estimated Slope	0.99 ± 0.39	1.12 ± 0.41*
Estimated Intercept	-67.5 ± 85.00	-94.10 ± 95.55*
Resistance Area product ($\frac{mmHg}{cm/s}$)	1.35 ± 0.71	1.11 ± 0.51*
Critical Closing Pressure(mmHg)	9.69 ± 23.91	0.78 ± 25.71*

Super index “*” represents the variables which are statistically different (*P<0.05) between the resting and CO₂ rebreathing states