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Reproduction of consistent pulse-waveform changes using a computational model of the cerebral circulatory system

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ABSTRACT

Due to the inaccessibility of the cranial vault, it is difficult to study cerebral blood flow dynamics directly. A mathematical model can be useful to study these dynamics. The model presented here is a novel combination of a one-dimensional fluid flow model representing the major vessels of the circle of Willis (CoW), with six individually parameterized auto-regulatory models of the distal vascular beds. This model has the unique ability to simulate high temporal resolution flow and velocity waveforms, amenable to pulse-waveform analysis, as well as sophisticated phenomena such as auto-regulation.

Previous work with human patients has shown that vasodilation induced by CO_2 inhalation causes 12 consistent pulse-waveform changes as measured by the morphological clustering and analysis of intracranial pressure algorithm. To validate this model, we simulated vasodilation and successfully reproduced 9 out of the 12 pulse-waveform changes.

A subsequent sensitivity analysis found that these 12 pulse-waveform changes were most affected by the parameters associated with the shape of the smooth muscle tension response and vessel elasticity, providing insight into the physiological mechanisms responsible for observed changes in the pulse-waveform shape.

1. Introduction

Assessing cerebral blood flow (CBF) dynamics for the care of brain injury patients is critical in order to titrate treatment, monitor brain states, and offer prognostic insights. Due to the inaccessibility of the cranial vault, it is difficult to directly study in humans the physiologic changes in response to different stimuli, in particular, the distal cerebrovascular changes. For example, differentiating between distal cerebral vasodilatation and vasoconstriction can potentially help establish a correct diagnosis of the causes of acute intracranial hypertension [1], acute neurological deterioration due to cerebral vasospasm [2,3], and cerebral metabolic crisis [4].

Recently, we conducted a series of investigations on how intracranial pressure (ICP) and cerebral blood flow velocity (CBFV) pulse-waveforms change when the cerebrovascular system is exposed to different stimuli. These studies considered changes in metrics derived from the heights and latencies of the sub-peaks of the pulse-waveform. One product of these investigations is an algorithm that can use continuously acquired ICP or CBFV pulses to detect cerebral vascular changes [5]. This algorithm is based on a key finding from our early work that particular intracranial pulse-waveform metrics consistently change, across patients and normal subjects [6], as the distal vasculature constricts or relaxes in response to carbon dioxide (CO_2) changes. This finding was based on the analysis of experimental data but it remains unexplained why the pulses behave in such a way. While a number of models of cerebral vasculature and autoregulation have been published [7–10], no model to our knowledge has simulated pulse-waveform trends as affected by cerebrovascular phenomena. The objective of this work is to develop a mathematical model and to investigate if it can reproduce the consistent pulse-waveform changes observed experimentally.

A wealth of literature describes models of CBF and ICP in terms of ordinary differential equations [11–16]. These models, by Ursino et al., account for the compliance and resistance created by blood vessels, the inward force of the cerebral spinal fluid as well, the

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ability of the vasculature to auto-regulate blood flow and the changes effected by varying blood CO_2 concentration. While this model is sufficiently sophisticated to describe the phenomena we are interested in the output cannot be analyzed at a pulse-waveform level.

Another model, described by Alastruey et al. in 2007, does simulate the cerebral blood flow on the pulse-waveform level [17]. This model represents the major vessels of the circle of Willis (CoW) as a one-dimensional deformable pipe network with axial blood flow. However, it uses a simplified three-element lumped parameter outflow model as a boundary condition for the terminal (outlet) vessel segment. This boundary condition addresses the viscous resistance of the blood moving through the vasculature and the compliance of the arterial walls, while ignoring the influence of ICP and the autoregulatory response of the distal vasculature to the changes of CBF. A subsequent model by Alastruey et al. did incorporate an autoregulatory boundary condition, but lacked a shared ICP model and the analysis focused on mean flow through the major cerebral vessels, not the specific pulse-waveform patterns.

In this paper, we present a novel combination of the pipe network model from Alastruey where the outlet boundary conditions are substituted with a modified version of the Ursino autoregulatory model and the ICP component of the autoregulatory model shared between all outlet vessels. This combination is advantageous in that it is sophisticated enough to simulate pulse-waveform changes in response to cerebrovascular dynamics, and by benefit of the one dimensional CoW model, reduces the computational requirement without a significant compromise in accuracy [18]. To validate this model, we utilized a sensitivity analysis to identify the model parameters with the most control over the transient pulse-waveform changes observed in CO_2 rebreathing experiments, and used these results to reproduce the vasodilation in the model.

2. Methods and materials

2.1. Overview of the multi-scale model

An electrical circuit analog of the model is presented in Fig. 1A. The corresponding equations for this model are presented in the supplementary materials. The model is composed of 3 sub-models: The pipe-flow model of the arteries of the neck and CoW, the autoregulatory model of the distal vascular beds, and the ICP model.

The arteries of the neck and CoW are modeled as a deformable pipe network, consisting of major cerebral vessels, with one dimensional flow in the axial direction of each vessel segment of interest. The temporal evolvements of the velocity and cross sectional area of each pipe (vessel) segment along its axial direction are numerically calculated based on flow dynamics equations. To construct the vascular network for the purpose of flow dynamics simulation, each segment's nominal cross-sectional area, length, and a β term, representing the vessel compliance, are defined; these parameters might be obtained from clinical measurements and with appropriate assumptions. The vessel parameters used for this model were adapted from Alastruey's work and are detailed in Table 1 [17,19]. The vascular model has three types of boundary conditions: Inlets, junctions between multiple vessel segments, and outlets. The input to this model is the volume flux through the vessel segments that represent the carotid and the vertebral arteries. This flux is calculated by multiplying the velocity measured via TCD by the nominal cross sectional area of the vessel. The measurable data from the model is the velocity of blood through the left and right: anterior cerebral arteries (ACAs), posterior cerebral arteries (PCAs) and middle cerebral arteries (MCAs).

The terminal flux from each outlet vessels is extrapolated and used as the input into its respective outlet model of the distal vascular bed. Similarly, the pressure at the entry to the outlet model is the pressure at the exit of the vessel. All of the outlet models are connected by a single ICP model. Parameters were shown in Table 2.

Table 1
The cross-sectional area, length, elasticity of each vessel in the 1D pipe flow model. As the model is symmetrical, each vessel is only listed once. Physiologic data based on previous modeling results by Alastruey et al. [17].

Vessel	Area (cm^2)	Length (cm)	Beta (m pa)
Common carotid artery	0.196	17.70	595.24
Internal carotid artery (*prox*)	0.126	17.70	944.83
Internal carotid artery (*dist*)	0.126	0.50	1889.66
External carotid artery	0.071	17.70	718.07
Middle cerebral artery	0.064	11.90	1360.56
Anterior cerebral artery (*prox*)	0.043	1.20	1096.00
Anterior cerebral artery (*dist*)	0.045	10.30	1133.80
Anterior communicating artery	0.017	0.30	718.07
Posterior communicating artery	0.017	1.50	680.28
Vertebral artery	0.058	14.80	642.49
Basilar artery	0.082	2.90	1511.73
Posterior cerebral artery (*prox*)	0.036	0.50	1020.42
Posterior cerebral artery (*dist*)	0.035	8.60	982.62

This model uses 24 vessel segments to describe the connectivity of the CoW (Fig. 1B), each with three parameters, and the six outlet models are defined by 20 parameters that interact non-linearly. Lastly the single ICP model has three parameters and serves to couple the outlet models. All parameter values for the outlet and ICP model were based on previous work by Ursino and Lodi [12]. The coupling of these components gives these model 195 degrees of freedom.

2.2. Consistent pulse-waveform changes during CO_2 challenge

To validate this model we attempted to reproduce the pulse-waveform response of the MCA CBFV associated with hypercapnic vasodilation. To study this process quantitatively, we utilized our recently developed MOCAIP algorithm [5]. MOCAIP is a framework for analyzing pulsatile signals such as CBFV and ICP. The algorithm works by extracting the individual pulses from a continuous signal and identifying the three sub peaks (P1, P2, and P3) and the respective valleys (V1, V2, V3) (Fig. 2). From these landmarks 128 pulse-waveform metrics are derived (Table 3).

Table 2
The baseline parameters for the six outflow model and the one ICP model.

Outlet model parameters	
r_0	0.015 cm
h_0	0.003 cm
σ_{e0}	0.143 mmHg
$K\sigma$	10.0
σ_{coll}	62.8 mmHg
T_0	2.16 mmHg cm
r_m	0.027 cm
r_t	0.018 cm
n_m	1.83 cm
η	232 mmHg s
K_g	1.43e6 $(mmHg\ s\ cm)^{-1}$
K_v	4.64e3 cm
τ	10 s
G	0.02 $mmHg^{-1}$
G_{pv}	1.14 $mmHg^{-1}\ s^{-1}$ ml
G_f	4.2e−4 $mmHg^{-1}\ s^{-1}$ ml
P_{an}	100 mmHg
q_n	12.5 ml s^{-1}
G_0	1.9e−3 $mmHg^{-1}\ s^{-1}$ ml
P_s	6.0 mmHg
Intracranial pressure model parameters	
K_e	0.11 ml^{-1}
C_m	0.2 $mmHg^{-1}$ ml
P_{icn}	9.5 mmHg