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Preface

It is a pleasure to welcome all participants of the 6th International Conference on Computational & Mathematical Biomedical Engineering to Sendai. This sixth edition is hosted by one of the most prestigious universities in Japan, Tohoku University.

CMBE is an important forum for sharing progress and knowledge within the community interested in engineering mathematics, computational and experimental methods applied to biomedical problems. This year's conference has received a large number of abstracts, each of which was peer-reviewed by members of the programme committee and mini-symposia organisers. We would like to thank all the authors and session organisers, committee members and external reviewers for their efforts.

The CMBE19 proceedings will be available to download from the [conference website](#). All authors are invited to submit an extended version of their paper to the '[International Journal for Numerical Methods in Biomedical Engineering](#)'.

The conference consist of an opening, 2 plenary and 6 keynote lectures, 23 tracks or mini-symposia divided into multiple sessions and 3 standard sessions. Poster abstracts are included in the conference programme and proceedings. CMBE also awards the 'International Journal for Numerical Methods in Biomedical Engineering (IJNMBE) Best PhD Award in Biomedical Engineering', in recognition of important contributions to the advancement of computational and/or mathematical biomedical engineering.

Finally, we would like to thank all delegates who attended CMBE19 and made its success.

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THE SELFISH-BRAIN HYPOTHESIS AS POSSIBLE CAUSE OF ARTERIAL HYPERTENSION: A MODELING STUDY

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SUMMARY

We use a global closed loop multiscale mathematical model of the human circulation to study a novel vascular hypothesis about the onset of essential hypertension. We extend the Müller-Toro model accounting for a precise cerebellum and brainstem vascular network, an autoregulation mechanism of brain hemodynamics, a detailed cerebrospinal fluid dynamics. We present preliminary computational results about the impact of some vascular cerebral anatomical malformations on cerebral perfusion and blood flow before the onset of arterial hypertension.

Key words: *Selfish brain hypothesis, vertebral artery hypoplasia, incompleteness of circle of willis*

1 INTRODUCTION

Arterial hypertension is by far one of the most important source of morbidity and mortality in the world, according to the World Health Organization [1]; it affects approximately 40% of the world population aged >25 years (1 billion people in 2008) and it has been estimated that complications of hypertension account for 9.4 million deaths worldwide every year. Essential, or primary, or idiopathic hypertension is historically defined as a rise in blood pressure. Multiple risk factors for arterial hypertension, including genetic variations, obesity, insulin resistance, high alcohol intake, and stress, have been identified but its etiology remains enigmatic in 95% of cases [2]. Despite well-established approaches to diagnosis and treatment (numerous classes of antihypertensives), fewer than half of all hypertensive patients have adequately controlled blood pressure.

The effect of arterial hypertension on the cerebrovascular structure is often described through the pathophysiology of vessel remodeling and decrease in luminal diameter leading to decreased blood flow. Recent groundbreaking medical research suggests that vascular anatomical variations may play a significant role in the onset of essential hypertension. In 1959, Dickinson and Thomason [3] hypothesized a significant correlation between narrowing of the vertebral arteries, brainstem hypoperfusion and development of arterial hypertension; cerebrovascular remodelling with a rise in resistance due to vasoconstriction of the supplying arteries to the brain may cause high blood pressure as a self-protective brain mechanism to preserve adequate levels of cerebral blood flow and perfusion. This mechanism is known as the "Selfish-Brain Hypothesis" or Cushing's mechanism [4]. The first confirmation focused on conscious humans about this theory was presented in 2016 by Warnert et al. [5]; a series of retrospective, mechanistic case-control, magnetic resonance imaging studies in a range of participants with different levels of blood pressure and classifications of hypertension were performed, supporting that congenital cerebral vascular variations, such as decreased vertebral artery diameters and variants in the posterior circle of Willis, are tightly coupled to the development of arterial hypertension and may play an important role in triggering high blood pressure.

The aim of this paper is to explore this theory *in silico* by means of mathematical modeling in the context of a global approach to human circulation.

2 METHODOLOGY

2.1 Mathematical model

The mathematical model used in this work to simulate the selfish brain hypothesis is an extension of the closed-loop model for the entire human circulation presented in Müller and Toro [6]. It includes networks for major arteries and veins (a total of 307 vessels) where a one-dimensional model consisting in a non-linear hyperbolic PDE system is used and solved using a high-order well-balanced non-linear numerical scheme in space and time based on ADER (Arbitrary high-order DERivatives) finite volume scheme for networks of elastic and viscoelastic vessels [7] and a local time stepping (LTS) approach [8]. The global model includes also lumped-parameter modelling for the heart and pulmonary circulation and for microvasculature (arterioles, capillaries and venules); moreover, the Starling-resistor like behaviour of the cerebral veins and the presence of venous valves are considered.

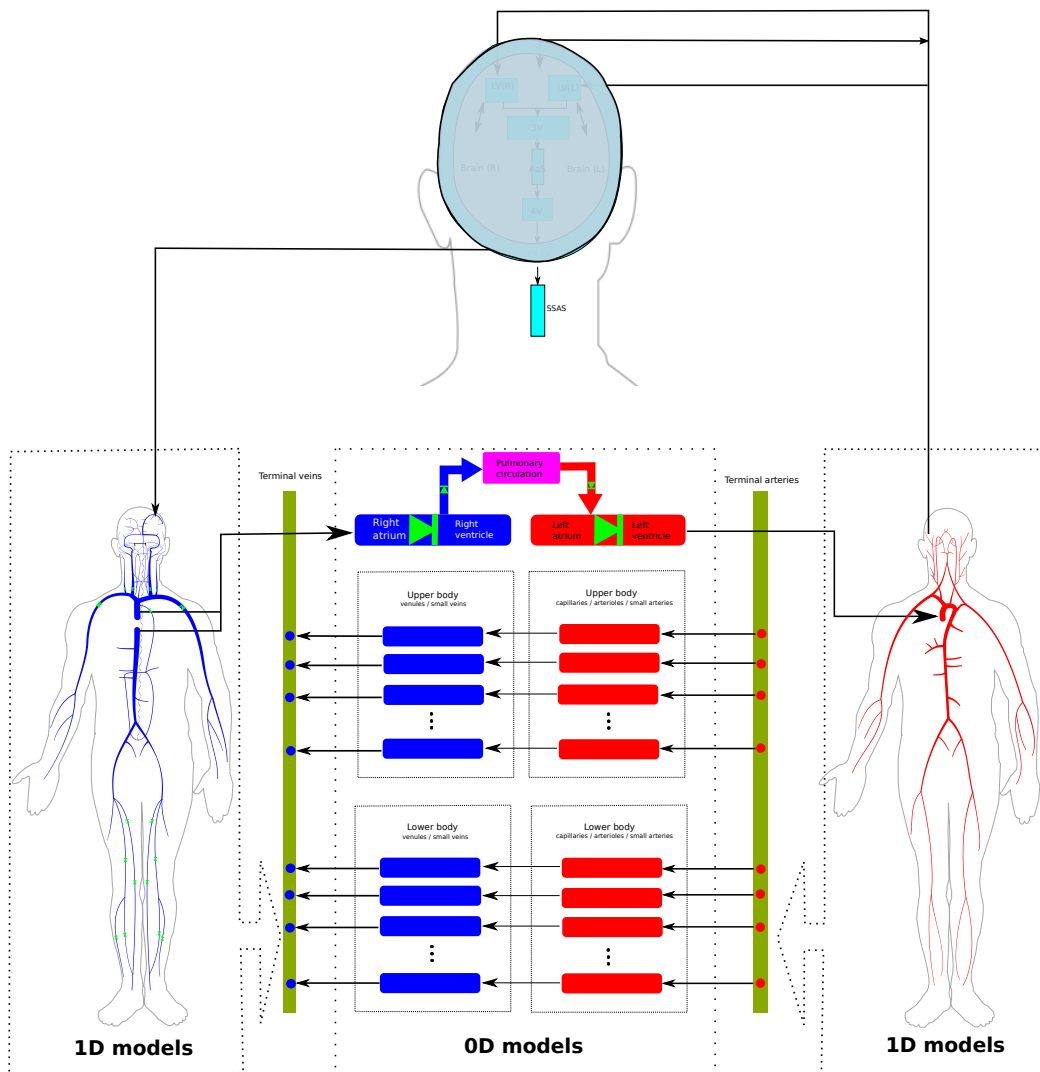


Figure 1: Schematic representation of the Müller-Toro global model.

Because of the medical problem under consideration, we consider a cerebral autoregulation model that simulates static regulation of brain perfusion and accounts for deviations from baseline cerebral flow in terminal cerebral vessels of the model and also for hyper- and hypocapnia [9]. Finally, the cerebral circulation is coupled to a refined cerebrospinal fluid model [10] which includes cerebral ventricles, aqueduct of Sylvius, cranial and spinal subarachnoid spaces.

2.2 Cerebral arterial network and its congenital variations

The cerebral arterial network with major cerebral arteries is shown in Figure 2(a). The brain is supplied by the circle of Willis, a circulatory anastomosis that is fed by four major vessels, the right and left internal carotid arteries (ICAs) and the right and left vertebral arteries (VAs) which converge to form the basilar artery. As concerning the posterior regions of the brain, we extend the cerebral vasculature, including superior cerebellar arteries (SCA), anterior (AICA) and posterior (PICA) inferior cerebellar arteries which arise respectively from the basilar and the vertebral arteries and supply the brainstem and cerebellum.

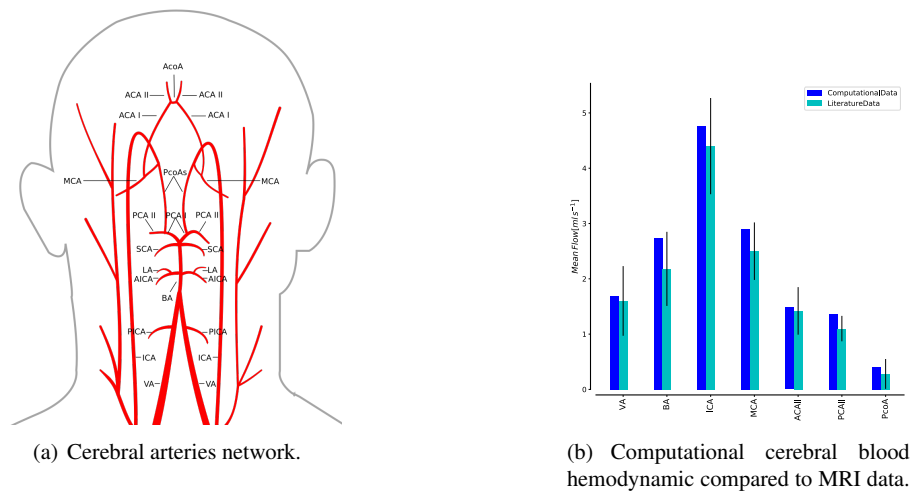


Figure 2: ICA: internal carotid artery; VA: vertebral artery; BA: basilar artery; ACA: anterior cerebral artery; MCA: middle cerebral artery; PCA: posterior cerebral artery; AcoA: anterior communicating artery; PcoA: posterior communicating artery; SCA: superior cerebellar artery; AICA: anterior inferior cerebellar artery; PICA: posterior inferior cerebellar artery; LA: labyrinthine artery.

The hypothesis put forward by Warnert et al. [5] is studied by changing our arterial network accordingly. Congenital variations in the arrangement and size of the vertebral arteries are common, ranging from asymmetry to severe hypoplasia (VAH). There is no consensus on a standard value to define VAH due to the absence of pathological symptoms. Recently, it was defined as a lumen diameter of ≤ 2 mm and a concomitant diameter asymmetry ratio $\leq 1:1.7$ in the course of the vertebral artery [11]. In this work, we consider different cases of hypoplasia until the critic case of 75 % of occlusion uniformly throughout the vessel. Since VAH is generally found more frequently on the right side, we put our attention only on the right vertebral artery. Other anatomical variations underlined by Warnert concern the incompleteness of the Circle of Willis (CoW). In this work we define an incomplete anterior CoW as absence of the first tract of anterior cerebral artery or absent anterior communicating artery, while an incomplete posterior CoW is defined as absence of unilateral or bilateral posterior communicating arteries or first segment of posterior cerebral artery or a combination thereof. Finally, the combination of VAH and the incompleteness of CoW is examined.

To assess the role played by these anatomical anomalies on a normotensive patient, we perform a computational study looking at their impact on cerebral perfusion (evaluated as the difference between mean arterial pressure and intracranial pressure), cerebral blood flow (total and regional), cerebral vascular resistance, cerebral autoregulation, pressure of major systemic arteries and cardiac output.

3 RESULTS AND CONCLUSIONS

When a complete CoW and normal size of VAs are considered, our model well-reproduces the cerebral blood hemodynamic compared to MRI literature data [12] (Figure 2(b)), with a total amount of cerebral blood flow equal to 12 ml/s. As suggested by Warnert et al. [5], we observe computationally that incomplete anterior circle of Willis does not produce relevant variation in cerebral perfusion because the remaining vessels are able to fully compensate for flow. Instead, vertebral artery hypoplasia and/or the incompleteness of the posterior part of the circle show variations in cerebral blood flow and perfusion, with a rise of vascular resistance (evaluated as the ratio between regional perfusion and blood flow). Major effects can be observed in the posterior parts of the brain; we underline the importance of the vasculature of the brainstem and cerebellum, where there is the vasomotor center but, more importantly, the cardiovascular and respiratory centers that play a key role in maintaining blood pressure homeostasis and other cardiac functions [13]. Despite cerebral hypoperfusion and increased cerebrovascular resistance, there is no significant rise in blood pressure. However, changes in cerebral perfusion of the posterior brain could be crucial in activation of the sympathetic nervous system and control mechanism of blood pressure, leading to rise systemic pressure to preserve adequate levels of cerebral blood flow and oxygen [14].

We have used a state of the art global model of the human circulation to explore the validity of the recent medical hypothesis on the triggering of essential hypertension. The confirmation of the Cushing's mechanism should potentially suggest early treatments of hypertension to prevent the progression of the disease and at the same time avoid ischemic stroke in the posterior brain and vascular dementia. The work is limited to the disease onset and does not consider the development of hypertension because we would like to assess the effects of cerebral malformations before the rise of systemic pressure. For the sake of completeness, future work will require the implementation of modeling strategies to simulate hypertension development, which in turn implies dealing with body fluids balance (mass transport and exchange, organ functioning, etc.), systemic regulatory mechanisms and arterial system remodeling.

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