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Brain venous haemodynamics, neurological diseases and mathematical modelling. A review

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ABSTRACT

Behind Medicine (M) is Physiology (P), behind Physiology is Physics (P) and behind Physics is always Mathematics (M), for which I expect that the symmetry of the *quadruplet* MPPM will be compatible with the characteristic bias of hyperbolic partial differential equations, a theme of this paper. I start with a description of several idiopathic brain pathologies that appear to have a strong vascular dimension, of which the most prominent example considered here is multiple sclerosis, the most common neurodegenerative, disabling disease in young adults. Other pathologies surveyed here include retinal abnormalities, Transient Global Amnesia, Transient Monocular Blindness, Ménière's disease and Idiopathic Parkinson's disease. It is the hypothesised vascular aspect of these conditions that links medicine to mathematics, through fluid mechanics in very complex networks of moving boundary blood vessels. The second part of this paper is about mathematical modelling of the human cardiovascular system, with particular reference to the venous system and the brain. A review of a recently proposed multi-scale mathematical model then follows, consisting of a one-dimensional hyperbolic description of blood flow in major arteries and veins, coupled to a lumped parameter description of the remaining main components of the human circulation. Derivation and analysis of the hyperbolic equations is carried out for blood vessels admitting variable material properties and with emphasis on the venous system, a much neglected aspect of cardiovascular mathematics. Veins, unlike their arterial counterparts, are highly deformable, even collapsible under mild physiological conditions. We address mathematical and numerical challenges. Regarding the numerical analysis of the hyperbolic PDEs, we deploy a modern non-linear finite volume method of arbitrarily high order of accuracy in both space and time, the ADER methodology. *In vivo* validation examples and brain haemodynamics computations are shown. We also point out two, preliminary but important new findings through the use of mathematical models, namely that extracranial venous strictures produce chronic intracranial venous hypertension and that augmented pressure increases the blood vessel wall permeability.

1. Introduction

Recent medical research [135] has established a strong association between extracranial venous anomalies, such as stenoses, and a range of diseases with no cure and unknown cause, affecting the central nervous system, such as multiple sclerosis (MS).

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The findings have generated, on the one hand, considerable controversy with the established, dominant autoimmune theory of MS, and on the other, have helped focus increasing attention from medical researchers on the venous system, a largely neglected district of the human vascular system. At first sight, the statement that a venous stenosis in one internal jugular vein outside the brain could trigger and explain the inflammation process linked to the destruction of the protective myelin layer of axons inside the brain, might seem far fetched. However, the description of the possible chain of events linked to extracranial venous anomalies is appealing and unfolds like this: extracranial venous strictures hamper the return of venous flow toward the heart and generate disturbed flow and intracranial venous hypertension. The flow disturbance hypothesis has been verified through measurements [135] and computation [15,89]. However the hypothesis of intracranial venous hypertension remains to be proved. Pressure measurements (usually invasive) in extracranial districts are supportive of the venous hypertension hypothesis, but no direct measurements inside the brain in connection with the reported extracranial venous anomalies have been published in the literature. As a matter fact such hypothesis is denied in the recent work of Meyer–Schwickerath et al. [81], where the authors use an *indirect* method to estimate the intracranial venous pressure and it is unclear what percentage of their MS patients had extracranial venous anomalies. On the other hand, Müller and Toro [87,89] have just reported computed results for the venous pressure inside the brain and found that this is higher if extracranial venous strictures exist. In the study they used their recently constructed mathematical model for the entire human circulation. These results await confirmation through measurements. Therefore, if the venous hypertension hypothesis is true, then it is reasonable to expect increased permeability of the blood-brain barrier (BBB), that selectively keeps blood separate from tissue in the central nervous system (CNS). Penetration of T cells from the blood stream into the brain, an accepted fact, would then cause an attack on the myelin, as a natural response from the immune system. On the other hand, the biophysics of disturbed flow would cause oscillatory wall shear stresses and transient stagnant flow that could trigger a complex biochemical set of events involving iron transport, deposition and inflammation.

The proposed chain of events is indeed very complex and its ultimate elucidation remains a formidable challenge to medical researchers and most probably will involve a multidisciplinary approach. But medical researchers have little time to wait for rigorous derivation of proofs. They have already tried and tested a potential treatment for extracranial venous strictures, the most obvious one, namely the removal of the venous strictures. This procedure has the elegant name of PTA (Percutaneous Transluminal Angioplasty) and preliminary results show promise, though much remains to be investigated [136,138,142].

The venous link to MS has attracted much attention and has contributed to the construction of a more unified approach to the study of several neurological diseases. For example, it is coming to light that even Idiopathic Parkinson's disease (IPD) may have a distinct vascular component, more precisely a venous component [75]. Hearing pathologies of unknown origin, such as Ménière's disease (MD), have attracted the attention of researchers. In fact there are several very recent studies in which it is demonstrated that MD is strongly associated to extracranial venous strictures [7,14,47]. In [14] PTA was applied, with encouraging results, both from the clinical and biophysical points of view. Other pathologies that have been associated to venous strictures include: retinal abnormalities [1], Transient Global Amnesia (TGA) [24] and Transient Monocular Blindness (TMB) [25]. See [59] for a review.

These medical research developments have brought in a physiological framework strongly rooted in the interacting mechanics of fluids and solids associated with the human circulation, generating fruitful discussion of plausible explanations of the various events at work. However, what is needed at this stage is quantitative research of the phenomena using all currently available tools, such as advanced magnetic resonance imaging (MRI), sonography and computed tomography (CT). Moreover, these biophysical processes are, in principle, amenable to mathematical modelling and computation. Such line of research is beginning to emerge, though much work remains to be done to overcome many challenges. The first challenge concerns basic knowledge of the brain venous system; this knowledge is lacking. Veins are tremendously deformable (highly non-linear, in mathematical terms), they collapse even under very mild physiological conditions, let alone pathological conditions, which are the ones of real interest, from a medical point of view. The geometry is difficult to obtain, physical parameters are largely unknown and are highly variable from subject to subject. The formulation of mathematical models is still in its developmental stage, the design of accurate and robust numerical methods to solve the equations is still in need of further progress. New schemes to treat the junctions of vessels, especially under critical conditions, need to be developed.

This paper consists of essentially two parts. The first part addresses several medical conditions and describes their basic physiology and potential link to the vascular system and thus to cardiovascular mathematics. In the second part we deal with mathematical modelling and associated hyperbolic equations. The rest of this paper is structured as follows. In Section 2 we review MS; in Section 3 we address the resurfacing of the vascular theory of MS; in Section 4 we describe the use of PTA to remove venous strictures; in Section 5 we describe other neurological diseases linked to the venous system; in Section 6 we discuss mathematical modelling of the human circulation, including equations and their mathematical analysis; in Section 7 we address the question of realistic blood flow models and some of the challenges; in Section 8 we address the subject of numerical methods; in Section 9 we discuss computational brain haemodynamics and show some results. We end up with concluding remarks in Section 10.

2. Multiple sclerosis: Brief review

In this section we succinctly review the main aspects of MS, starting with a simplified description of the disease. The reader may find a more comprehensive description of MS in [100] and the many relevant references therein. Technical definitions of MS as well as some historical notes are included in this section, which is supplemented with a description of the BBB.