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Identifying the myogenic and metabolic components of cerebral autoregulation

S.J. Payne

Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford, Parks Road, Oxford OX1 3PJ, UK

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ABSTRACT

Cerebral autoregulation is the term used to describe a number of mechanisms that act together to maintain a near constant cerebral blood flow in response to changes in arterial blood pressure. These mechanisms are complex and known to be affected in a range of cerebrovascular diseases. However, it can be difficult to assign an alteration in cerebral autoregulation to one of the underlying physiological mechanisms without the use of a complex mathematical model. In this paper, we thus set out a new approach that enables these mechanisms to be related to the autoregulation behaviour and hence inferred from experimental measurements. We show that the arteriolar response is a function of just three parameters, which we term the elastic, the myogenic and the metabolic sensitivity coefficients, and that the full vascular response is dependent upon only seven parameters. The ratio of the strengths of the myogenic and the metabolic responses is found to be in the range 2.5 to 5 over a wide range of pressure, indicating that the balance between the two appears to lie within this range. We validate the model with existing experimental data both at the level of an individual vessel and across the whole vasculature, and show that the results are consistent with findings from the literature. We then conduct a sensitivity analysis of the model to demonstrate which parameters are most important in determining the strength of static autoregulation, showing that autoregulation strength is predominantly set by the arteriolar sensitivity coefficients. This new approach could be used in future studies to help to interpret the components of the autoregulation response and how they are affected under different conditions, providing a greater insight into the fundamental processes that govern autoregulation.

1. Introduction

The brain is one of the most tightly regulated organs in the human body, with cerebral blood flow being matched both locally and globally to metabolic needs through a number of different mechanisms. One of the most important aspects of control is that cerebral blood flow is maintained near constant over a wide range of arterial blood pressure (ABP): this is known as cerebral autoregulation [1], first quantified by Lassen [2] in its static form. Later studies then explored the dynamic response to changes in ABP, determining its characteristic biphasic response [3]. In response to decreases in ABP, CBF shows a rapid decrease due to the immediate reduction in ABP; this is then followed by a rise caused by feedback mechanisms that act to increase arteriole vessel diameter and hence to reduce resistance to flow. The steady state result is that the fractional decrease in CBF is much smaller than that in ABP.

The physiological processes that act to adjust arteriolar diameter are essentially a balance between vasoconstricting and vasodilating factors that set the phosphorylation of smooth muscle cells in the walls of the arterioles. By adjusting the stiffness of these cells through a number of feedback pathways, the relationship between radius and pressure is altered allowing the vasculature to establish a new equilibrium state in response to changes in ABP. These vessels are then one component of the cerebral vasculature that can be characterised in terms of a relationship between changes in arterial blood pressure and changes in cerebral blood flow (or more often cerebral blood flow velocity, CBFV, due to the fact that transcranial Doppler, the most commonly used measurement technique, actually only measures flow velocity, most commonly in the middle cerebral artery). This relationship is often modelled using the instantaneous relationship:

$$V = \frac{P_a - P_c}{RAP} \tag{1}$$

where CBFV is denoted by V, arterial blood pressure, ABP, by P_a, critical closing pressure, CrCP, by P_c, and resistance-area product, RAP, by RAP. The product of resistance and area results from the use of CBFV, rather than CBF, in Eq. (1).

E-mail address: stephen.payne@eng.ox.ac.uk

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Nomenclature

f	fraction
f_a	resistance fraction of large arterial vessels
f_r	resistance fraction of regulating vessels
f_v	resistance fraction of venous vessels
F	force
h	wall thickness
k	stiffness
p	pressure
q	flow
r	radius
RAP	resistance-Area Product
S	sensitivity coefficient
S_E	elastic sensitivity coefficient
S_M	myogenic sensitivity coefficient
S_V	metabolic sensitivity coefficient
Δ	change
λ	stretch
σ	stress
τ	shear stress
∇	gradient
$\mathcal{R}$	resistance

The critical closing pressure thus represents the intersection with the x axis on a plot of CBFV changes against ABP changes and it has received considerable attention [4], with a number of methods being used to estimate it experimentally, see for example [5]. A number of studies have also quantified the contributions of the myogenic and metabolic mechanisms to the parameters in Eq. (1), showing that RAP appears to be associated primarily with the myogenic mechanisms and that CrCP is primarily associated with the metabolic mechanisms [6], although there is some cross-over. Other studies have investigated how this is affected in subject populations, for example with the myogenic response being found to be impaired in acute ischaemic stroke patients [7].

To help in interpreting cerebral autoregulation, a number of physiological models have been proposed, see [8–16] and others. These models have adopted a wide range of complexity, although nearly all use the same fundamental concepts with an equivalent electrical circuit and a feedback mechanism that adjusts arteriolar stiffness (or compliance); some also consider the neural response as well as the autoregulation behaviour, for example [14]. Many of them have been partially validated using experimental data, although there is rarely sufficient data to validate all of the different parameter values used in the model, given the complexity of the response. Their complexity also makes it difficult to consider their behaviour explicitly in terms of the myogenic and metabolic components of the response and hence to relate to studies into these parameters.

We therefore take a different approach here, by considering the autoregulation response to comprise a simple balance between a vasoconstricting (myogenic) mechanism and a vasodilating (metabolic) mechanism that act on the arteriolar bed within the context of a simple electrical equivalent model. The aim of this approach is essentially to help to interpret the balance between the two mechanisms that control vascular tone through the construction of a mathematical model of autoregulation. This, much simpler, approach enables us to examine the relative influences of the myogenic and metabolic responses more directly, particularly in a way that can be compared with experimental data. The aim is to identify the relative strengths of the two components without going into further detail about the pathways, such that they can be related directly to experimental data.

It should be noted that we associate the myogenic response with vasoconstriction and the metabolic response with vasodilation in our terminology here, as will be explained below. We do this for simplicity, although it is likely that the responses are a mixture of these pathways: if preferred the responses could be thought of as the responses governed by direct stress and shear stress respectively (as will be presented below).

The use of the mathematical model proposed here enables us to provide a means for interpreting experimental data in a more rigorous manner; through the use of experimental data, it could then be possible to separate out the two components and to understand how they link to experimental measurements that can be routinely made. This will then allow for changes in this balance to be identified more easily, helping to interpret the different components that act to maintain cerebral blood flow and thus to identify their relative importance, in particular how this balance is altered in diseased states. The aim is that this will help to drive treatment of impaired autoregulation through a better understanding of precisely what it is that is impaired under different conditions.

2. Theory

We note at the start that we will only consider static autoregulation here, for simplicity. It would be possible in future to adapt the proposed static model to a dynamic one.

2.1. Single vessel model

We thus begin by considering a single arteriole in steady state. The Laplace law relates wall stress, σ, to internal pressure, p, radius, r, and wall thickness, h:

$$\sigma = \frac{pr}{h} \tag{2}$$

For small changes about a baseline point, denoted by Δ, this can be written in the form:

$$\Delta\sigma^* = \Delta p^* + \Delta r^* - \Delta h^* \tag{3}$$

where we use the star superscript to denote a value as a fraction of its baseline value. Note that throughout the paper we are primarily concerned with variables as fraction of their baseline values: this is done to simplify the analysis since it reduces very substantially the number of variables in the resulting equations.

Similarly, the wall force can be related to internal pressure and radius:

$$F = pr \tag{4}$$

and hence:

$$\Delta F^* = \Delta p^* + \Delta r^* \tag{5}$$

We then assume that this force is dependent in some (as yet unspecified) way upon the smooth muscle cell stiffness (which will be related to the level of phosphorylation), k, and the stretch, λ, giving:

$$\Delta F^* = S_{F,k}\Delta k^* + S_{F,\lambda}\Delta\lambda^* \tag{6}$$

where the stretch is related to changes in radius:

$$\Delta\lambda^* = S_{\lambda,r}\Delta r^* \tag{7}$$

through geometric considerations. Note that we use $S_{i,j}$ here to denote the sensitivity of variable i to variable j. We also assume that the volume of the vessel wall remains constant and that hence:

$$0 = \Delta r^* - \Delta h^* \tag{8}$$

We then assume that the stiffness responds to two stimuli, one related to stress and one to shear stress, with these acting in opposite directions:

$$\Delta k^* = S_{k,\sigma}\Delta\sigma^* - S_{k,\tau}\Delta\tau^* \tag{9}$$