THE ROLE OF OXYGEN IN CEREBROVASCULAR CONTROL: A MATHEMATICAL ANALYSIS

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***Abstract*- A former model of cerebrovascular regulation and intracranial pressure dynamics has been improved to account for the effect of oxygen lack on cerebral vessels and cerebral blood flow (CBF). Model assumes that CBF regulation is the result of three distinct feedback mechanisms working on pial arteries and arterioles: they represent CO_2 reactivity, tissue hypoxia, and a mechanism (either pressure-dependent or flow-dependent in nature) that does not depend on O_2 or CO_2 directly. With a suitable choice of the mechanism gains, assigned by means of an automatic best-fitting procedure, the model is able to reproduce the pattern of inner radii in small and large pial arteries and CBF during hypoxia and hypotension quite well. These results suggest that autoregulation to perfusion pressure changes cannot be explained merely on the basis of tissue hypoxia, but it requires the presence of further flow-dependent response at the level of small arterioles. Finally, model simulations suggest that acute hypoxia, in a patient with reduced cerebrospinal fluid (CSF) outflow, may induce a significant increase in intracranial pressure, with the risk of secondary brain damage. The model may be of value to improve the present understanding of cerebrovascular control in a large range of clinical conditions.**

***Keywords* – autoregulation, cerebral blood flow, hypoxia.**

I. INTRODUCTION

It is well-known that oxygen plays a significant role in cerebrovascular regulation in several conditions of clinical importance. Hypoxia is a significant vasodilator of cerebral vessels, leading to an increase in cerebral blood flow as high as 200-300% when PaO_2 is reduced below 25 mmHg. Moreover, the oxygen lack is involved in cerebral blood flow adjustments during reduction in cerebral perfusion pressure (autoregulation), increase in tissue metabolism, cerebral ischemia, hemodilution. Kontos et al. [1] demonstrated that oxygen acts on cerebral vessels mainly through an indirect mechanism, mediated by the release of vasodilatory susbstances in the perivascular space, rather than by a direct action on vascular smooth muscle. Nevertheless, the exact importance of oxygen in the control of cerebral hemodynamics vs. other putative mechanisms (myogenic, neurogenic, shear-stress etc.) is still insufficiently known.

In previous years we formulated a mathematical model of cerebrovascular regulation and intracranial dynamics in men, able to account for several results of clinical relevance [2,3]. In this model, however, the effect of oxygen in the control of cerebral vessels was not explicitly considered. Hence, the model could not be used to simulate maneuvers in which hypoxia is the primary stimulus, nor the role of O_2 during autoregulation could be assessed.

Aim of this work is to present an improved version of the same model, in which the function of oxygen in modulating pial arteries regulatory response is explicitly considered. The model may be of value to improve our understanding of the mechanisms regulating cerebral blood flow in a broader range of clinical conditions, including hypoxia, metabolic changes and hemodilution.

II. METHODOLOGY

The model of intracranial hemodynamics and cerebrospinal fluid circulation is the same as in previous studies [2,3]. Hence, it is not described again for briefness.

Regulation mechanisms are assumed to work on two vascular segments arranged in series: the large pial arteries (subscript j = 1) and pial arterioles (j = 2). The effect of regulation is taken into account by means of an activation factor M_j, which locally modulates smooth muscle tension.

In the present model, three distinct regulatory actions are assumed to work on each segment: they represent CO_2 reactivity, tissue hypoxia, and further possible mechanisms involved in cerebral autoregulation. The latter might represent myogenic or neurogenic regulation, endothelium dependent factors, or a direct effect of blood flow washout on perivascular vasodilatory metabolites.

The block diagram in Fig. 1 shows how the different regulatory mechanisms modulate the activation factor. Each mechanism acts through a static gain ($G_{CO_2,j}$, $G_{O_2,j}$ and $G_{aut,j}$, respectively), which set the mechanism strength, and a low-pass dynamic with time constant τ ($\tau_{CO_2,j}$, $\tau_{O_2,j}$ and $\tau_{aut,j}$, respectively). Finally, the mechanisms interact non-linearly through a sigmoidal relationship.

As shown in the upper branch of Fig. 1, any increase in arterial CO_2 pressure causes a decrease in the activation factor, hence vasodilation. The opposite occurs during hypocapnia. The third branch in Fig. 1 describes the action of mechanisms, which do not depend on CO_2 and O_2 directly. According to previous studies [2,3], we assumed that large and medium pial arteries (first segment) are mainly controlled by a pressure-dependent mechanism, which causes vasodilation during a decrease in cerebral perfusion pressure. Conversely, small pial arteries (second segment) are controlled by a flow-dependent mechanism, which vasodilates when CBF is reduced below normal. All equations for the first and third branch in Fig. 1 can be found in previous papers.

The oxygen mechanism is new compared with previous works, hence its main mathematical aspects will be described in greater detail thereafter.

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Abstract

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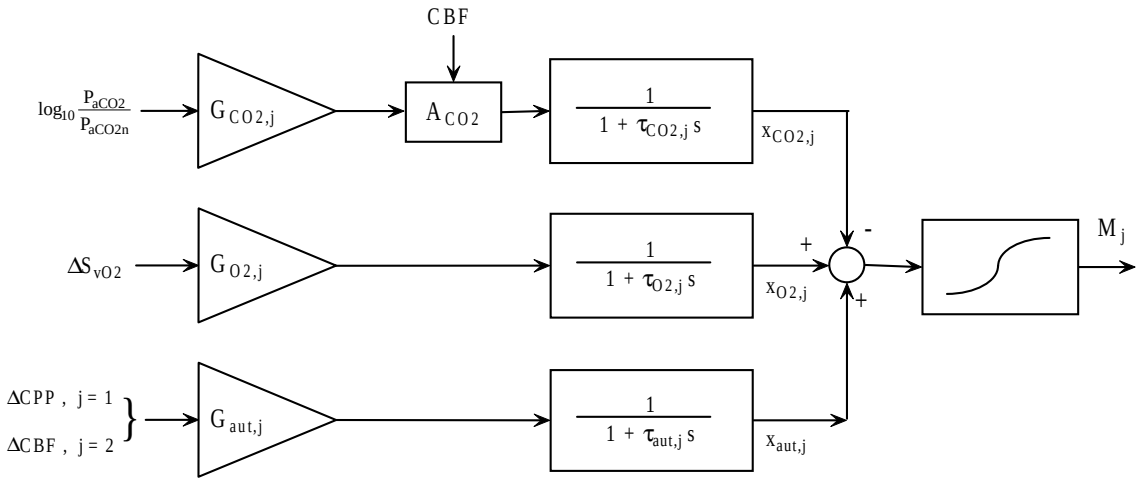

Fig. 1. Block diagram describing the regulatory actions included in the model. ACO2 represents an attenuation term which depresses CO2 reactivity during ischemia [3]. See text for the meaning of other symbols.

Oxygen – According to Kontos et al. [1], O_2 acts on pial vessels mainly through an indirect mechanism, mediated by hypoxia of the neural cells. Hence, we assumed that the smooth muscle activation factor depends on O_2 saturation in venous blood. This choice is reasonable since, at least as a first approximation, venous O_2 saturation reflects the oxygen level in tissue.

Venous oxygen concentration is computed by assuming a mass balance between oxygen delivery by cerebral blood flow and the oxygen consumption rate of the entire brain, i.e.,

$$C_{v,O_2} = C_{a,O_2} - \dot{M}_{O_2} / q \qquad (1)$$

where q is cerebral blood flow, C_{a,O_2} and C_{v,O_2} are O_2 concentration in the arterial and venous blood, respectively, and $\dot{M}_{O_2}$ is brain oxygen consumption rate. The latter quantity is assumed to remain constant, at its basal level, throughout the present simulations. Venous saturation is computed from concentration, by neglecting the amount of oxygen dissolved in venous blood.

O_2 concentration in the arterial blood is computed, as a function of oxygen arterial pressure (which is an input quantity for the model) by using the following well known equation

$$C_{a,O_2} = \alpha_{O_2} \cdot P_{a,O_2} + C \cdot S(P_{a,O_2}) \qquad (2)$$

where α_{O_2} is the oxygen solubility coefficient in blood, P_{a,O_2} is arterial oxygen pressure, C is the oxygen binding capacity of blood, and $S(P_{a,O_2})$ is the hemoglobin-oxygen saturation. The latter was described by means of the Hill model, i.e.

$$S(P_{a,O_2}) = \frac{(P_{a,O_2}/P_{50})^n}{1+(P_{a,O_2}/P_{50})^n} \qquad (3)$$

where P_{50} is the value of arterial oxygen pressure at which hemoglobin is 50% saturated (P_{50} = 26 mmHg in men), and n is approximately 2.7 for human blood.

In conclusion, the second branch in Fig. 1 implies that any decrease in venous oxygen saturation below normal causes smooth muscle relaxation and vasodilation, in an effort to restore a more appropriate oxygen level in brain tissue.

Mechanism interaction – The three mechanisms delineated above interact in a non-linear way in the computation of the activation factor. In fact, as shown in Fig. 1, the individual regulatory actions are not simply summed, but, after summation, are passed through a sigmoidal relationship with upper and lower saturation levels. The central point of the relationship corresponds to normal smooth muscle activation. The upper saturation level corresponds to maximal activation, while the lower saturation level signifies that smooth muscle is completely relaxed, hence its active tension is zero.

The use of a sigmoidal relationship allows conditions of exhausted cerebrovascular reserve to be simulated.

All parameters characterizing intracranial dynamics and cerebral hemodynamics have been given in order to mimic the behavior of a normal man. A description of these parameters, with numerical values, can be found in previous works [2,3]. The gains of feedback mechanisms have been given through an automatic procedure (Nelder-Mead algorithm) in order to fit experimental data from the physiological literature.

III. Results

In this work, the model is used to simulate CBF and pial vessel response to different levels of hypoxia and hyperoxia, at constant perfusion pressure, and the response to changes in cerebral perfusion pressure during normoxia (autoregulation). In order to compare model results with those of the existing literature, which use the open skull or pial window preparation, all trials were performed with an extremely low value of the intracranial elastance coefficient (k_e = 0.0001 cm^{-1} instead of the normal value 0.11 cm^{-1}). This means to have an enormous intracranial compliance. Moreover, during all trials arterial $PaCO_2$ was maintained constant at its basal level; hence the CO_2 mechanisms do not affect the regulatory

response. The results thus depend on the assignment of 4 mechanism gains, i.e., $G_{O_2,1}$, $G_{aut,1}$, $G_{O_2,2}$ and $G_{aut,2}$. The values of these parameters were assigned through an automatic fitting procedure. To this end, we minimized a least square criterion function of the difference between model predictions and experimental data (Fig. 2). As it is clear from this figure, model provides a good agreement of experimental results both during hypotension and hypoxia. Parameters describing CO_2 reactivity were also given with a minimization procedure. Results are not reported for briefness.

In the previous figures the simulations were performed using a very high value of intracranial compliance, in order to mimic experiments performed with the pial window procedure. It is now interesting to analyze the effect that vasodilation, induced by hypoxia, may have on intracranial pressure (ICP) and cerebral perfusion pressure in real closed-skull conditions. This analysis may be of clinical value, especially with reference to neurosurgical patients (such as head injured patients) with reduced intracranial compensatory reserve (low intracranial compliance and impaired CSF outflow) who are prone to cerebral ischemia and secondary brain damage. An example is shown in Fig. 3. Here we simulated the ICP time pattern during a gradual severe hypoxia (down to approximately 30 mmHg) associated with ventilatory hypocapnia (down to 32 mmHg) in a hypothetical patient with reduced CSF outflow. The time patterns of PaO_2 and $PaCO_2$ used as inputs to the model are presented in the upper panel, while the corresponding ICP time pattern is shown in the middle panel. It is worth noting the progressive increase in ICP up to 30 mmHg, and the rapid return toward the initial level at the cessation of the hypoxic stimulus. Both input quantities and the ICP response agree with tracings reported in the clinical literature [4].

IV. Discussion

The present study represents a significant extension of previous models of intracranial dynamics. The main new aspects can be recapitulated as follows: i) Results of the best-fitting procedure stress that tissue hypoxia is not the sole responsible of small pial artery vasodilation during hypotension. In order to achieve correct reproduction of experimental data, the presence of additional pressure-dependent and flow-dependent mechanisms must be hypothesized. These mechanisms may be myogenic, neurogenic or endothelium-dependent. This result agrees with the common observation that autoregulation can be significantly depressed in the severe head injury, a result which could be explained with difficulty on the basis of metabolic mechanisms only. ii) Acute hypoxia in neurosurgical patients may be extremely dangerous not only owing to its primary effect (i.e., a reduction of O_2 delivery to neural tissues) but also due to its secondary consequences (mainly, an increase in ICP induced by the rise in cerebral blood volume and in cerebrospinal fluid production). This may lead to serious secondary brain damages, especially in patients with reduced CSF outflow and/or reduced intracranial compliance.

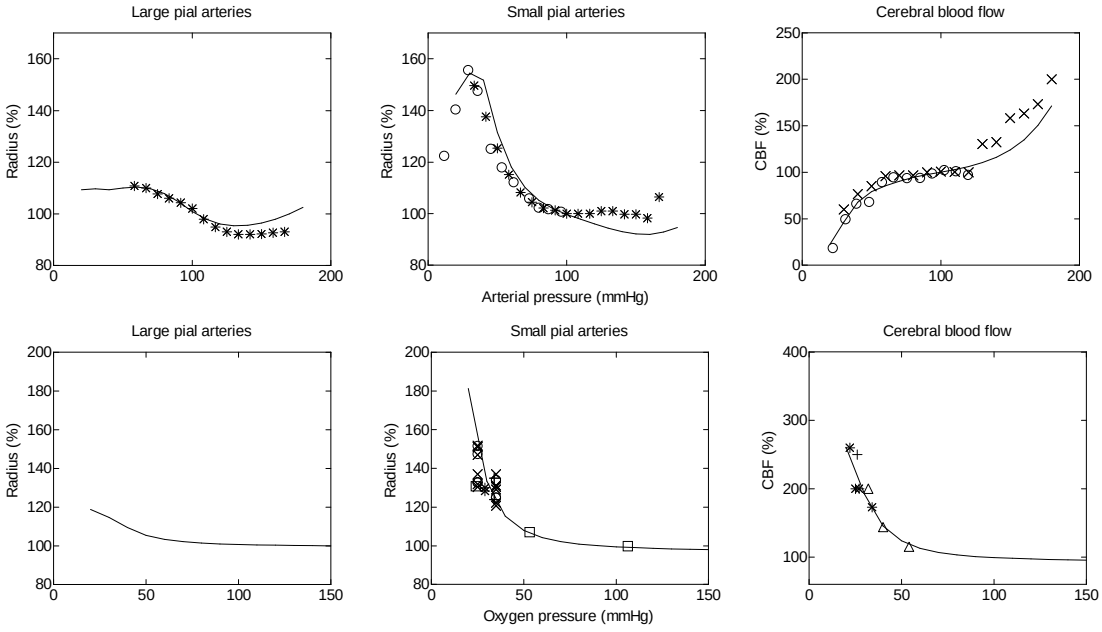

Fig. 2. Inner radius percentage changes in large and small pial arteries, and CBF percentage changes plotted vs. systemic arterial pressure during normoxia (upper panels) and vs. arterial oxygen pressure during normotension (lower panels). Continuous lines are model simulation results. Experimental points are from: *Autoregulation, radii*: * [5] in cats; o [6] in cats. *Autoregulation, CBF*: o [6] in cats; x [7] in rats.- *Hypoxia, radii*: □ [1] in cats; * [8] in cats; o [9] in newborn pigs; x [10] in sheep fetus; + Wilderman and Armstead [11] in newborn pigs. *Hypoxia, CBF*: * [12] in dogs; + [13] in dogs; △ [14] in cats.

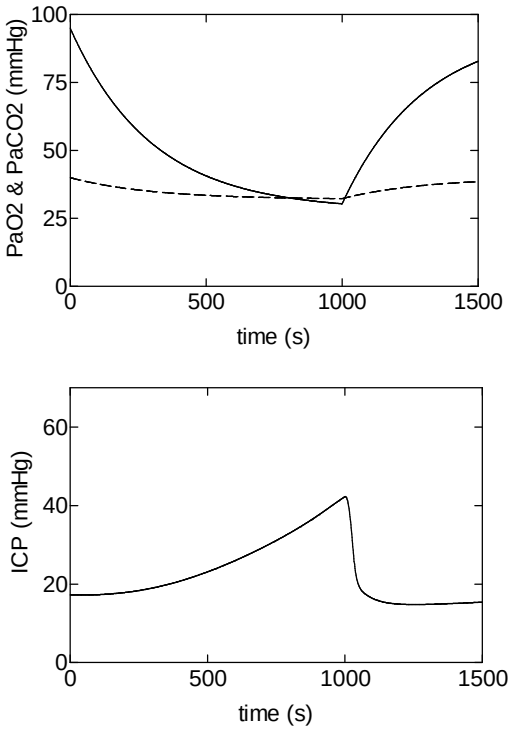

Fig. 3. Time pattern of ICP simulated with the model (lower panel) in a patient with reduced CSF outflow but normal intracranial compliance during a progressive poikilocapnic hypoxia (i.e., hypoxia with reduced $PaCO_2$) followed by a progressive restoration of the normal respiratory level. The pattern of arterial oxygen pressure and arterial CO_2 pressure used as input to the model are shown in the upper panel.

V. Conclusion

The present study confirms that the model is able to reproduce the interaction among multiple mechanism working simultaneously, hence it can be applied to the analysis of intracranial dynamics in a broad spectrum of clinical conditions. Moreover, the model clarifies the specific role of tissue hypoxia vs. other mechanisms in the control of CBF: Among the additional perturbations that the model can mimic faithfully (but which are not shown here for briefness) we can mention hemodilution, hypoxia+hypercapnia, and hypercapnia+hypotension.

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