



A Mathematical Model of Intracranial Pressure and Cerebral Hemodynamics Response to CO₂ changes

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Abstract

Alterations in blood CO₂ tension (p_{aCO_2}) are frequently used in neurosurgical Intensive Care Units to manage patients with severe brain diseases and to test the status of mechanisms regulating cerebral blood flow.

In this work, the complex relationships between p_{aCO_2} , cerebral blood volume, cerebral blood flow and intracranial pressure (ICP) are investigated by means of an original mathematical model. The model incorporates the intracranial compliance, the cerebrospinal fluid production and reabsorption processes, the collapse of the terminal cerebral veins, and the active response of large and small cerebral arteries to perfusion pressure changes (autoregulation) and to changes in p_{aCO_2} (chemical regulation).

Two different kinds of simulations have been performed to validate the model and to test its possible clinical usefulness. In a first stage, ICP was maintained constant to mimic experiments with the open skull and the cerebrovascular response to changes in systemic arterial pressure and in p_{aCO_2} was reproduced. The results of the model show that agreement with the experimental curves of various authors is quite good.

In the second stage, conditions occurring with a closed skull were simulated. These are characterized by acute changes in ICP, induced by active changes in cerebral blood volume. In these conditions, the model was used to reproduce the time pattern of ICP and blood flow velocity at the level of the middle cerebral artery observed in patients during alterations in systemic arterial pressure and p_{aCO_2} . A comparison between simulation results and real tracings is presented and discussed.

The model may represent a valid tool to interpret the complex relationships between cerebral hemodynamic quantities in neurosurgical Intensive Care Units.



102 Simulations in Biomedicine IV

1 Introduction

It is well known that CO_2 is one of the strongest modulator of cerebral blood flow (CBF) [1]: an increase in arterial carbon dioxide tension ($p_{a\text{CO}_2}$), i.e. hypercapnia, can produce a marked vasodilation of the cerebral vasculature, while a reduction in $p_{a\text{CO}_2}$ (hypocapnia) causes a strong vasoconstriction. Indeed, the modulation of the level of $p_{a\text{CO}_2}$ in neurosurgical Intensive Care Units is a usual technique to manage patients with severe acute brain damage: the induced hypocapnia, in fact, tends to hold intracranial pressure (ICP) at a low level in patients with intracranial hypertension; on the other hand, hypercapnia is used as a test to analyze the effectiveness of the mechanisms regulating cerebral blood flow. In general, cerebral vessel reactivity to $p_{a\text{CO}_2}$ correlates well with the outcome of patients with severe head injury [2].

Furthermore, acute changes in cerebral blood volume, induced by cerebral regulatory actions (not only CO_2 reactivity, but also autoregulation to perfusion pressure alterations), can have a dramatic impact on the time pattern of ICP, through a mechanism known as the “*vasodilatory cascade*” [3].

The interrelationships between intracranial pressure, cerebral blood volume changes and cerebral hemodynamics were studied by means of original mathematical models in some previous reports [4-6]. The approach with mathematical models has revealed itself very useful to reach a major comprehension of the complex relationships among intracranial quantities and, in perspective, to provide information to help diagnosis and therapy in neurosurgical Care Units.

Aim of this work is to extend and improve the previous model to include the dependence of the intracranial hemodynamics on the level of $p_{a\text{CO}_2}$ and to analyze the relationships between $p_{a\text{CO}_2}$ reactivity, cerebral autoregulation and intracranial pressure changes.

This work is organized as follows. First, model structure is described in qualitative terms and the new equations simulating CO_2 reactivity and autoregulation are presented. Then, the model is used to simulate the results of physiological experiments on response of pial arteries at different levels of systemic arterial pressure (SAP) and $p_{a\text{CO}_2}$ [7-14]. Finally, we test the capability of the model to simulate real tracings of ICP and middle cerebral artery velocity (MCAV) in patients with severe brain diseases, adjusting a set of parameters of clinical relevance.

2 Model description

The model of the intracranial pressure dynamics represents an extension of a previous one. It includes the arterial-arteriolar cerebrovascular bed, the

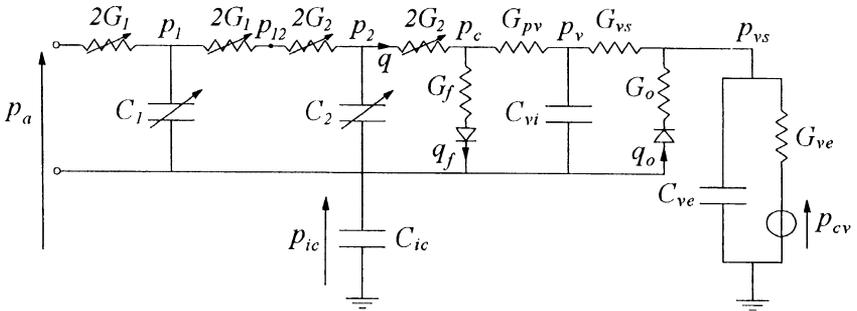


Figure 1: Electric analog of the intracranial dynamics. G_1 , C_1 and G_2 , C_2 : hydraulic conductance and compliance of proximal and distal cerebral arteries, respectively; p_a : arterial pressure; p_1 and p_2 : intravascular pressure at the level of large pial arteries and medium and small arteries, respectively; q : cerebral blood flow; p_c , p_v : capillary and cerebral venous pressures; p_{vs} , p_{cv} : sinus venous and central venous pressures; p_{ic} : intracranial pressure; C_{ic} : intracranial compliance; G_{pv} , C_{vi} : hydraulic conductance and compliance of large cerebral veins; G_{vs} : hydraulic conductance of terminal intracranial veins; G_{ve} , C_{ve} : hydraulic conductance and compliance of the extracranial venous pathways; G_f , G_o : conductances to CSF formation and CSF outflow; q_f , q_o : rates of CSF formation and CSF outflow.

dynamics of cerebrospinal fluid (CSF), the intracranial elasticity, the cerebral venous bed and the cerebrovascular regulatory mechanisms. These aspects are not substantially changed. A more detailed analysis of the equations, their origin and significance can be found in previous reports [4, 5]. As a new aspect, we have added equations concerning the reactivity of the arterial-arteriolar vessels to p_{aCO_2} and its interaction with autoregulation.

The fundamental principle on the basis of the intracranial dynamics is the *Monro-Kellie doctrine*, which establishes the constancy of the overall cranio-spinal volume, in spite of variations in its single components. The electric analog of Figure 1 represents the interactions between the individual intracranial volumes, according to the model.

Any change in a volume within the intracranial space causes a compression or a shifting of the remaining portions with an intracranial pressure alteration. This behavior determines the storage capacity of the craniospinal system, usually described with a monoexponential pressure-volume curve [15]: as a consequence, the intracranial compliance results inversely proportional to ICP, through a constant parameter called the *elastance coefficient*.

104 Simulations in Biomedicine IV

The pial arterial-arteriolar compartment has been subdivided into a series of two segments: the first represents the large pial arteries (proximal arteries), while the second describes the medium and small pial arteries (distal arteries) down to brain capillaries. This distinction is justified by the different response of the two segments to autoregulation stimuli [7] and to p_{aCO_2} changes [10]. Each segment is described by a *Wind-Kessel model*, characterized by a hydraulic resistance, which takes into account the pressure drop and the viscous energy losses, and a hydraulic compliance, reproducing the changes in blood volume. Both these quantities depend on the value of vessel inner radius, which, in turn, is affected by the cerebral autoregulation and the reactivity to p_{aCO_2} . The inner radius can be calculated starting from the *Laplace law*, which states the equilibrium of forces acting on the vessel wall:

$$p_j \cdot r_j - p_{ic} \cdot (r_j + h_j) = T_{ej} + T_{vj} + T_{mj}; \quad j = 1 \text{ or } 2 \quad (1)$$

where the subscript $j = 1$ indicates a quantity or a parameter of the proximal arteries, while the subscript $j = 2$ refers to arterioles; p_j is the intravascular pressure; p_{ic} is the extravascular (that is intracranial) pressure; h_j is wall thickness; T_{ej} , T_{vj} and T_{mj} denote elastic, viscous, and smooth-muscle tensions, respectively. Elastic tension is described by an exponential function of the inner radius, while viscous tension linearly depends on the radius time derivative. According to the data reported in [16], we have adopted the following campanular expression for the muscular tension:

$$T_{mj} = T_{m0j} \cdot (1 + M_j) \cdot \exp\left(-\left[\frac{r_j - r_{mj}}{r_{tj} - r_{mj}}\right]^{n_{mj}}\right); \quad j = 1 \text{ or } 2 \quad (2)$$

where r_{mj} is the value of radius at which the muscle cells exert a maximal tension; T_{m0j} is the corresponding optimal active tension; r_{tj} and n_{mj} are constant parameters. Finally, M_j is an activation factor of smooth muscle contractility: the value $M_j = 0$ indicates basal conditions, when $M_j > 0$ we have active vasoconstriction, while $M_j < 0$ is associated to active vasodilation.

M_j is the result of two contributions, x_{jaut} and x_{jCO_2} , which describe the effect of autoregulation and the reactivity to p_{aCO_2} , respectively. These terms are not simply summed to give M_j , but they enter in a sigmoidal curve:

$$M_j = \frac{\min_j + \max_j \cdot \exp\left[\frac{(x_{jaut} + x_{jCO_2})}{k_{\sigma j}}\right]}{1 + \exp\left[\frac{(x_{jaut} + x_{jCO_2})}{k_{\sigma j}}\right]}; \quad j = 1 \text{ or } 2 \quad (3)$$

where \min_j and \max_j are the lower and upper saturation levels, respectively, and $k_{\sigma j}$ is a constant parameter which permits to set the central slope.

It is worth noting that, as a consequence of the sigmoidal curve, the two feedback mechanisms interact in a non-linear way.

The terms x_{jaut} and x_{jCO_2} are state variables, the dynamics of which is described by means of low-pass transfer function:

$$\begin{aligned}\frac{dx_{1aut}}{dt} &= \frac{1}{\tau_{1aut}} \cdot [-x_{1aut} + G_{1aut} \cdot (p_a - p_{an} - p_v + p_{vn})] \\ \frac{dx_{1CO_2}}{dt} &= \frac{1}{\tau_{1CO_2}} \cdot [-x_{1CO_2} - G_{1CO_2} \cdot \log_{10}(p_{CO_2} / p_{CO_{2n}})] \\ \frac{dx_{2aut}}{dt} &= \frac{1}{\tau_{2aut}} \cdot [-x_{2aut} + G_{2aut} \cdot (q - q_n) / q_n] \\ \frac{dx_{2CO_2}}{dt} &= \frac{1}{\tau_{2CO_2}} \cdot [-x_{2CO_2} - G_{2CO_2} \cdot \log_{10}(p_{CO_2} / p_{CO_{2n}})]\end{aligned}\tag{4}$$

where τ_{jaut} , τ_{jCO_2} , G_{jaut} , G_{jCO_2} are the time constants and the central gains of the mechanisms acting on the j th segment; p_a , p_v , p_{aCO_2} , q are systemic arterial pressure, cerebral venous pressure, arterial CO_2 tension and cerebral blood flow, respectively; and the subscript n is used to indicate the basal value of each quantity.

The previous equations deserve some comments: while the reactivity to p_{aCO_2} differs in proximal arteries and arterioles only as to the strength and time delay, but it is described by an identical mechanism, the distinction in the cerebral autoregulation involves also the nature of the feedback action. In fact, according to some authors [7], we assumed that the autoregulatory mechanism on proximal arteries is pressure-dependent, whereas that acting on small arterioles is activated by flow-dependent factors. Furthermore, the reaction to carbon dioxide is proportional to the decimal logarithm of the p_{aCO_2} to take into account that CO_2 mainly affects smooth muscle tension through pH changes in the perivascular space.

The circulation from cerebral capillaries to intracranial veins is represented by a hydraulic resistance and a compliance. Since the effect of the regulatory mechanisms on cerebral veins is negligible, we assumed that venous bed behaves passively. Hence, venous compliance has been taken as inversely proportional to the local transmural pressure value. Furthermore, we have included the phenomenon of passive collapse of terminal intracranial veins (bridge veins and lateral lakes) during intracranial hypertension, through a mechanism similar to that of a *Starling resistor*. The remaining drainage pathways down to the heart are described through a *Wind-kessel*, composed of the resistance and the compliance of the extracranial veins.

We have assumed that both the processes of CSF production at the cerebral capillaries and CSF outflow at the dural sinuses are passive and

106 Simulations in Biomedicine IV

unidirectional: that is, they are proportional to the corresponding transmural pressure value until the latter remains positive, otherwise they fall to zero.

Finally, a value for the middle cerebral artery velocity is calculated dividing the portion of CBF at this level of circulation (about one third of total) by the vessel internal section. The value of the middle cerebral artery inner radius is a function of the transmural pressure, as experimentally observed [17].

3 Results

The model is of the ninth order: the state variables are the intracranial pressure, the cerebral venous pressure, the dural sinus pressure and, for each of the segments of arterial-arteriolar bed, the inner radius and the terms which express the autoregulation and the reactivity to p_{aCO_2} (Eqs. 4).

A basal value for model parameters describing CSF circulation and intracranial elasticity has been taken from clinical data [see 4, 5]. Parameters describing pial vessel response to regulatory stimuli, not directly measured on humans, have been derived from physiological literature [7-14].

Model equations have been numerically solved on a 486 MS-DOS personal computer, using the *Runge-Kutta-Felberg 4/5 method* with automatic stepsize adjustment.

The simulations have been divided in two stages. In the first we have reproduced the results of physiological experiments performed with the dura opened at constant ICP. To this end, we have assigned an extremely low value, practically zero, to the intracranial elastance coefficient.

Figure 2 (left panel) presents the pattern of inner radii in large and small pial arteries and of cerebral blood flow evaluated at different values of mean arterial pressure. The model results, obtained in steady state conditions, are compared with those experimentally found during physiological studies in animals [7-9]: the agreement is quite good. We can see that the large pial arteries are mostly active for moderate alteration of the mean arterial pressure, where the response of the small pial arteries is modest: this is the region in which the autoregulatory action is mainly efficient. In fact, cerebral blood flow does not substantially change in the range 60-150 mmHg, according to various authors [1,9]. If SAP decreases under the lower limit of autoregulation, the pial arterioles exhibit an evident vasodilation associated with an enlargement of the cerebrovascular volume; at the same time, CBF rapidly decreases. It is noticeable that the inner radii behave in a completely passive way for very low or very high SAP values.

In the right panel of Figure 2 we report the dependence of the same quantities on p_{aCO_2} . The vasoconstriction which occurs in the cerebrovascular bed during hypocapnia is evident: the effect appears more pronounced than that caused by autoregulation; the cerebral blood flow is reduced to half its normal value. During hypercapnia, a vasodilation is produced and CBF can reach a two-fold increase. The comparison between simulation results and the

corresponding experimental data [10-14] proves to be suitable. Also in this case, the amount of vessel variation is smaller in the large pial arteries than in the medium and small ones: i.e. the carbon dioxide reactivity is dependent on vessel size, as demonstrated in [10].

We have also analyzed the interaction between autoregulation and p_{aCO_2} reactivity, varying SAP and p_{aCO_2} together. The results, not reported in this

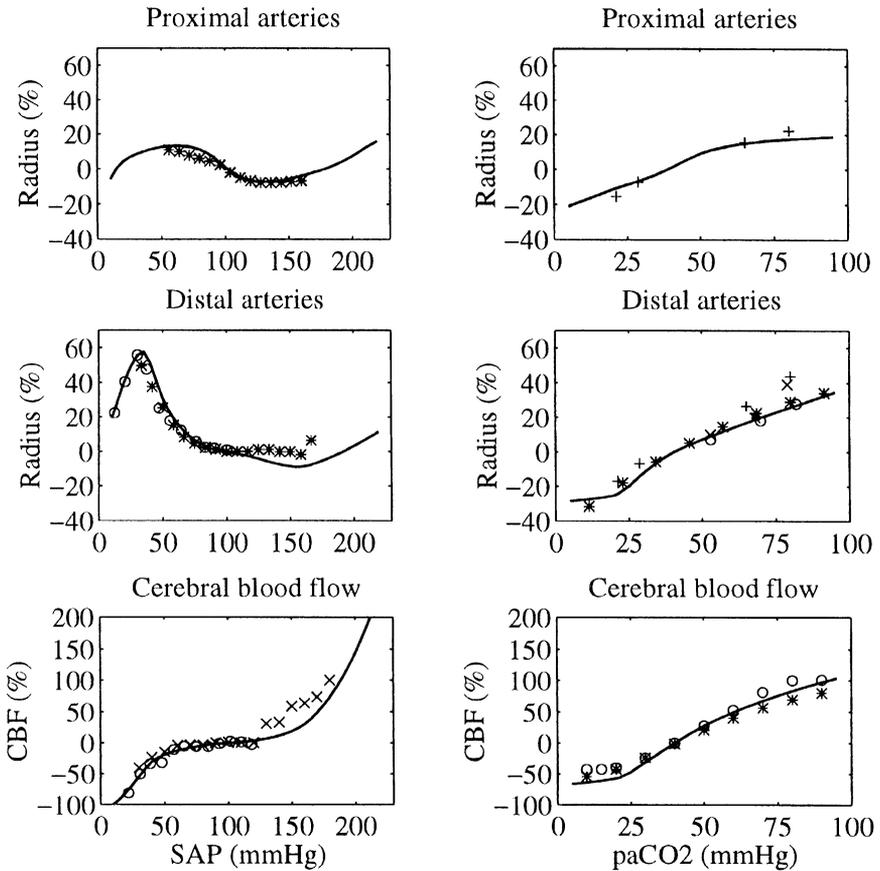


Figure 2: Left panel: pattern of inner radii in large and small pial arteries and of cerebral blood flow versus mean SAP. Model results (solid line) are compared with experimental data obtained by Kontos et al. [7] (*), MacKenzie et al. [8] (o) and Harper et al. [9] (x). Right panel: pattern of inner radii in large and small pial arteries and of cerebral blood flow versus p_{aCO_2} . Experimental data are obtained by Wei et al. [10] (+), Raper et al. [11] (*), and Lavoisier et al. [12] (o, x) in case of the radii; by Reivich et al. [13] (*) and Harper et al. [14] (o) as regards CBF.

108 Simulations in Biomedicine IV

paper, show that an increase in hypercapnia reduces the autoregulatory capacities of the cerebrovascular bed [1], while arterial hypotension progressively eliminates the vasodilatory effect of hypercapnia [14].

In the second stage of the simulation, intracranial dynamics has been studied in a closed skull, assuming that the intracranial pressure is free to change. The model equations have been used to analyze real tracings measured in a group of patients with acute brain damage. The intracranial pressure and the middle cerebral artery velocity were monitored during variations of p_{aCO_2} and SAP levels: patients were normally held in hypocapnia, by means of mechanical hyperventilation; normal CO_2 levels were restored by CO_2 inhalation at steady ventilation; alterations in SAP were induced by modulating a continuous infusion of norepinephrine. In order to reproduce the experimental data, we had to adjust some parameters of the model, keeping the others at their basal value. The set of the estimated parameters includes the CSF outflow resistance, the intracranial elastance coefficient, the gains and the time constants of the regulatory actions (Eqs. 4) and the blood volume in pial arterioles. In most cases, a satisfactory conformity between simulation results and real tracings has been attained.

Figure 3 shows the results concerning one of the analyzed patients. The subject starts in a condition of pronounced hypocapnia (the normocapnic value being at 40 mmHg) and, after some minutes, p_{aCO_2} is gradually increased. During the maneuver, arterial pressure nearly remains at a constant low level (Fig. 3a). The alteration of CO_2 causes a vasodilation which joins that due to arterial hypotension: as a consequence ICP rises (Fig. 3b). The velocity initially increases too with CO_2 until it reaches a maximal value, thereafter it remains quite constant or even lessens despite continuous CO_2 elevation and ICP rise.

Moreover, Fig. 3c and 3d show the dynamic relationships between ICP and p_{aCO_2} (Fig. 3c) and between ICP and MCAV (Fig. 3d), concerning the portion of the tracing delimited by the arrows in Fig. 3a (from minimal to maximal value of p_{aCO_2}). As regards Fig. 3c, we can note that, according to some authors [2], the curve ICP vs. p_{aCO_2} exhibits a monoexponential trend. This result can be partly imputed to the exponential pressure-volume relationship of the craniospinal compartment and partly to the interaction between ICP and autoregulation. In fact, the ICP rise amplifies the action of autoregulation via a lowering of cerebral perfusion pressure (“*vasodilatory cascade*”), until maximal vasodilation is reached.

Finally, the ICP/MCAV relationship (Fig. 3d) can be divided into two parts, having different slopes. In the initial one, MCAV grows more than ICP: i.e., the rise in p_{aCO_2} can actually increase CBF despite ICP changes. Beyond an upper limit of CO_2 (*inflexion point*), instead, the curve becomes quite vertical: the blood flow regulation is exhausted, due to the antagonism between ICP increase and cerebral vasodilation. In this condition maximal blood flow is reached despite a further decrease in cerebrovascular resistance.

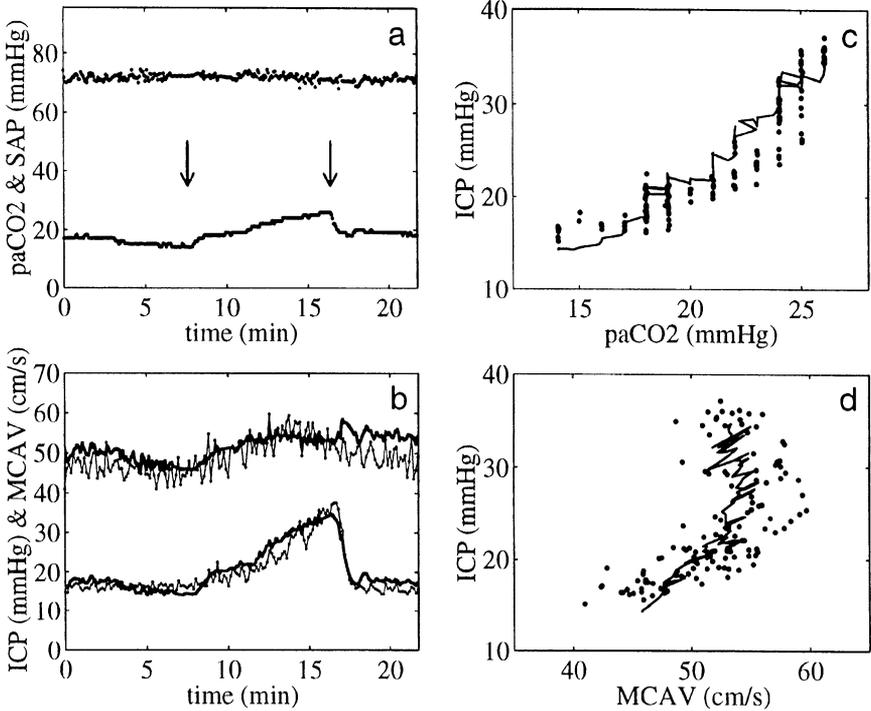


Figure 3 : Left upper panel: time pattern of SAP (upper curve) and paCO_2 (lower curve) in one of the analyzed patient. Left lower panel: time pattern of MCAV (upper curves) and ICP (lower curves); model response (solid line) are compared with clinical data (dotted line). Right panel: relationships between ICP and paCO_2 (above) and between ICP and MCAV (below); model results (solid line) are compared with clinical data (dots).

4 Discussion

In this work, we offer a quantitative outlook of the main factors which regulate cerebral blood flow, and of their relationships with the other components of the craniospinal system (namely, intracranial elasticity and cerebrospinal fluid circulation). The motivation for such a study is that understanding the connections between cerebrovascular reactivity and ICP is of primary importance for the management of patients in neurosurgical Intensive Care Units. Maneuvers which cause vasoconstriction and reduce CBF, in fact, may be of therapeutic value to lessen ICP in subjects at risk of intracranial hypertension; however, improper maneuvers may induce excessive CBF reduction, or cause disproportionate increases in ICP through a *vasodilatory cascade*, with danger of *cerebral ischemia* and *secondary brain damage*.



110 Simulations in Biomedicine IV

The study was composed of two different stages, with the emphasis on physiological and clinical results, respectively. In the first stage, basal parameters were assigned to the model in order to reproduce cerebrovascular reactivity observed in experiments on animals. The results emphasize that large and small pial arteries exhibit a different response, the smaller vessels being able to vary their caliber to a much greater degree than the larger ones. As a consequence, relevant cerebral blood volume changes may occur within the craniospinal compartment during massive arteriolar vasodilation. Moreover, the results of Fig. 2 suggest that the active responses of the pial arterial-arteriolar vessels are able to wholly explain the observed CBF changes, and that the venous cerebrovascular bed plays a negligible role in the control of CBF.

In the second stage, the model was used to analyze the consequences that cerebrovascular active responses, induced by controlled stimuli, may have on the time pattern of ICP in neurosurgical patients. The main prediction of the model is that maneuvers which modify CBF may frequently cause serious changes in ICP, and that these changes depend on model parameters (hence, on the patient's condition) in complex non-linear ways.

Basically, there are two main mechanisms in the model by which the cerebrovascular response may affect ICP. Initially, one can observe an acute response caused by active blood volume changes within the craniospinal compartment. This response does not only depend on the strength of the regulatory mechanisms, but also on the amount of blood volume contained in pial arteriolar vessels and on the slope of the craniospinal pressure-volume relationship. Later, the ICP response is mainly affected by changes in CSF circulation, which, in turn, depends on CBF via a modulation of CSF production rate at the cerebral capillaries.

As a consequence of the multitude of factors affecting ICP, the model foresees a variety of possible kinds of behavior, which are reflected in different dynamical relationships between ICP, blood flow velocity, SAP and p_{aCO_2} . These predictions are supported by a comparison with ICP and blood velocity tracings monitored in patients with severe brain diseases. Even though only a single case has been presented here for the sake of brevity, we checked the capability of the model to reproduce clinical data on 10 different tracings drawn from 6 patients, including a variety of alterations in p_{aCO_2} and SAP. The results suggest that the model can represent a valid support for the interpretation of intracranial dynamics starting from routine measurements. In perspective, it might contribute to improvement of diagnoses and to establish target therapies in neurosurgical Intensive Care Units.



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