Cerebral hemodynamics during arterial and CO₂ pressure changes: in vivo prediction by a mathematical model

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Ursino, M., A. Ter Minassian, C. A. Lodi, and L. Beydon. Cerebral hemodynamics during arterial and CO₂ pressure changes: in vivo prediction by a mathematical model. Am J Physiol Heart Circ Physiol 279: H2439–H2455, 2000.—The aim of this work was to analyze changes in cerebral hemodynamics and intracranial pressure (ICP) evoked by mean systemic arterial pressure (SAP) and arterial CO₂ pressure (PₐCO₂) challenges in patients with acute brain damage. The study was performed by means of a new simple mathematical model of intracranial hemodynamics, particularly aimed at routine clinical investigation. The model was validated by comparing its results with data from transcranial Doppler velocity in the middle cerebral artery (VₐMCA) and ICP measured in 44 tracings on 13 different patients during mean SAP and PₐCO₂ challenges. The validation consisted of individual identification of 6 parameters in all 44 tracings by means of a best fitting algorithm. The parameters chosen for the identification summarize the main aspects of intracranial dynamics, i.e., cerebrospinal fluid circulation, intracranial elastance, and cerebrovascular control. The results suggest that the model is able to reproduce the measured time patterns of VₐMCA and ICP in all 44 tracings by using values for the parameters that lie within the ranges reported in the pathophysiological literature. The meaning of parameter estimates is discussed, and comments on the main virtues and limitations of the present approach are offered.

Carbon dioxide reactivity; intracranial pressure; cerebral autoregulation; severe brain damage; transcranial Doppler

CEREBRAL PERFUSION PRESSURE (CPP) and CO₂ pressure have a strong impact on intracranial vessels through the action of cerebrovascular control mechanisms (7, 13, 32). Under normal circumstances, a fall in blood pressure causes a rapid dilatation of resistance vessels, whereas a rise in blood pressure causes vasoconstriction (23, 26). As a consequence, cerebral blood flow (CBF) is maintained at the preexisting level in healthy subjects in the CPP range of 50–150 mmHg [a phenomenon named “autoregulation” (11)].

Moreover, arterial PₐCO₂ (PₐCO₂) is a strong vasodilator of the cerebral vasculature because it is able to increase CBF by 100% during severe hypercapnia (17, 37). The role of CO₂ is mainly mediated by pH changes in the perivascular space (11, 40).

The previous mechanisms, however, not only affect cerebral hemodynamics but also may have a serious impact on intracranial pressure (ICP) via complex nonlinear relationships (7, 16). First, cerebral circulation occurs within a closed space (the skull and neuroaxis); hence, alterations in cerebral blood volume (CBV) may modify ICP through the craniospinal pressure-volume relationship. Furthermore, CBF variations modulate the cerebrospinal fluid (CSF) production rate and ICP through changes in intracranial capillary pressure.

Knowledge of the previous relationships is of paramount importance for the treatment of patients with severe head injury in neurosurgical intensive care units. Decreasing CO₂ pressure through hyperventilation, in fact, is frequently used to reduce ICP in patients at risk of intracranial hypertension in whom cerebral vasculature is reactive (13, 35). Vasoconstriction, however, may induce an excessive fall in CBF, with the potential hazard of cerebral ischemia and secondary brain damage (32). Setting a correct level of mean systemic arterial pressure (SAP) is also controversial. Although some authors (2) in recent years proposed to maintain low SAP in head-injured patients to minimize the risk of cerebral edema, a more common opinion today is that CPP should be maintained >70–80 mmHg to avoid hypoperfusion and the consequent brain ischemia (7, 15, 36, 39). The danger of ICP instability (a phenomenon often called “vasodilatory cascade”) should also be considered when CPP approaches the autoregulation lower limit (38, 50).

This scenario is complicated by the observation that cerebrovascular control mechanisms may be impaired in head injury. Severe head trauma disturbs autoregulation in most patients (7, 13, 21, 35). Impairment in cerebrovascular reactivity, in turn, may be a consequence of the trauma per se, may be secondary to alterations in ICP and craniospinal storage capacity, or may occur during episodes of arterial hypotension with reduced CPP (15, 36).

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Because cerebral hemodynamics adjustments in head-injured patients are complex multifactorial phenomena, they may be better understood with the use of mathematical models and computer simulation techniques. Many such models have been presented in the previous decades, with the focus on different aspects of intracranial dynamics and cerebrovascular control (8, 20, 28, 49); however, none of them focused attention on the interaction among ICP, CBV, CSF circulation, and cerebrovascular control mechanisms.

In recent years we formulated a mathematical model of the relationships among ICP, CBV, and cerebrovascular control mechanisms in acute brain damage (50, 54). The model revealed itself able to reproduce ICP and cerebral hemodynamics in different conditions of clinical interest (50–52).

The previous model, however, is computationally too heavy to be routinely used in a clinical setting. The aim of this work is to describe and validate a simplified model that can incorporate the main mechanisms involved in intracranial dynamics and permit their quantitative individual assessment with a drastic reduction in mathematical complexity.

The paper is structured as follows. First, the qualitative aspects of the model are described. The clinical and computational methods used to test the validity of the model are then presented. The results concern the reproduction of ICP and middle cerebral artery (MCA) velocity tracings during SAP and PaCO2 challenges. Finally, the virtues and limitations of the obtained results are critically discussed.

**Qualitative Model Description**

The model presented in this paper is significantly simplified compared with that used in a previous recent work (54). The main simplifications are 1) that the model does not distinguish between the behavior of large and small pial arteries and 2) that the biomechanics of the pial arterial-arteriolar vascular bed are reproduced by means of a simple windkessel model (that is, the arrangement of a hydraulic resistance and a hydraulic capacity). By contrast, in previous works (50, 52, 54) the biomechanics of large and small pial arteries were described starting from the equilibrium of forces in the vessel wall, with wall elastic and active (muscular) characteristics taken into account.

The main aspects of the model are described in qualitative terms. All model equations, with considerations of numerical integration methods, are given in Appendix A. A biomechanical analog of the model is shown in Fig. 1.

**Intracranial Hemodynamics and Hydrodynamics**

*Large intracranial arteries.* The first segment in the model represents circulation in the basal intracranial arteries, down to and excluding the large pial arteries. The hemodynamics of this segment are described by means of a single hydraulic resistance (Rla). Because the impact of cerebrovascular regulation mechanisms on the basal intracranial arteries is quite small (14), Rla has been maintained constant throughout the simulations. An approximate estimation of blood flow velocity at an MCA (V MCA), to be compared with the results of transcranial Doppler (TCD), is computed by assuming that blood flow in an MCA is about one-third of total CBF. We can thus write

\[
V_{MCA} = k_v \cdot \frac{1}{3} \cdot \frac{q_{la}}{\pi \cdot R_{MCA}^2}
\]

where q_{la} is total CBF at the level of the basal intracranial arteries and \( R_{MCA} \) is MCA inner radius. Finally, \( k_v \) is a scaling factor that accounts for the slope of the Doppler probe relative to the vessel under examination and for the proportionality between average and maximum velocity in the section. In fact, the TCD technique measures maximum velocity, while the right-hand member of Eq. 1 (see Eq. A12 in the APPENDIX A) refers to mean time velocity.

The value of \( R_{MCA} \) is a function of cerebral artery transmural pressure (SAP – ICP) through a monoequational pressure-radius relationship taken from Hayashi et al. (19). This means that the MCA behaves passively and becomes progressively more rigid when transmural pressure increases. We are aware that the use of Eq. 1 may involve some errors. First, data reported by Hayashi et al. (19) concern human specimens in vitro, while the behavior of the vessel in vivo might be different. Moreover, head trauma may modify the pressure-radius characteristic of the MCA. Finally, changes in the velocity profile or the presence of cerebrovascular heterogeneity may alter the relationship between mean CBF and maximum velocity, thus making the coefficient \( k_v \) time dependent. All these differences might induce some errors in Eq. 1 and, hence, in the \( V_{MCA} \) prediction by the model.

*Pial arterial-arteriolar cerebrovascular bed.* The second segment in Fig. 1 simulates the pial arterial circulation, extending from the large pial arteries down to...

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*Fig. 1. Biomechanical analog of the mathematical model, in which resistances are represented with restrictions and compliances with bulges. P_a, systemic arterial pressure; P_{la} and R_{la}, pressure and resistance of large intracranial arteries, respectively; P_{par}, P_{cap}, and C_{par}, pressure, resistance, and compliance of pial arterioles, respectively; P_{cp}, capillary pressure; q_t, tissue cerebral blood flow; R_{pv}, resistance of proximal cerebral veins; C_{ct}, intracranial venous compliance; P_e, cerebral venous pressure; P_{ca} and R_{ca}, sinus venous pressure and resistance of the terminal intracranial veins, respectively; R_{v}, cerebral blood flow; q_{f}, CSF formation rate and CSF outflow rate, respectively; C_{pa}, and C_{cv}, intracranial pressure and intracranial compliance.*
and including small pial arteries and intraparenchymal arterioles. For the sake of simplicity, the model does not distinguish between hemodynamics in different-sized vessels; hence, we consider only one segment, characterized by its values of hydraulic resistance \( R_{pa} \) and compliance \( C_{pa} \). As described in Cerebrovascular Regulation Mechanisms, both parameters are actively regulated by cerebrovascular control mechanisms.

**Venous intracranial circulation.** The intracranial venous vascular bed is described by the series arrangement of two segments. The first extends from the small postcapillary venules down to the large cerebral veins and includes the venous resistance \( R_{pv} \) and the intracranial venous capacity \( C_{vi} \). Because the impact of cerebrovascular mechanisms on the venous vasculature is negligible and large veins do not collapse even at elevated ICP (3), venous resistance has been maintained constant throughout the simulations. By contrast, venous capacity is inversely proportional to the local transmural pressure level, which implies a monoexponential pressure-volume relationship for the veins. We are aware that the exact mathematical expression for venous compliance may be affected by the head injury. However, changes in intracranial venous transmural pressure are almost modest in our model (because of the Starling resistor mechanism described below); as a consequence, the exact expression for venous compliance has only a minor impact on the results.

The last segment in Fig. 1 represents the terminal intracranial veins (lateral lakes and bridge veins). During intracranial hypertension these vessels collapse or narrow at their entrance into the dural sinuses, with a mechanism similar to that of a Starling resistor (50). Because of this mechanism, pressure in the large cerebral veins \( (P_c) \) remains a little higher than ICP even during elevated intracranial hypertension (provided ICP < SAP).

**CSF circulation.** The circulation of CSF is described as a passive process. CSF is produced at the cerebral capillaries because of a positive transmural pressure gradient \( (P_c - P_{ic}) \), where \( P_c \) is capillary pressure and \( P_{ic} \) is intracranial pressure) and is reabsorbed at the dural sinuses because of a negative transmural pressure gradient \( (P_{vs} - P_{ic}) \), where \( P_{vs} \) is venous sinus pressure). The resistances to CSF formation and CSF outflow are \( R_f \) and \( R_{pv} \), respectively. However, both processes are unidirectional, so we have assumed that resistances rise to infinity when the corresponding transmural pressure is reversed.

**Intracranial compliance.** Because the overall intracranial volume must remain constant, any change in the content of one of the previous compartments (i.e., pial artery volume at \( C_{pa} \), venous volume at \( C_{vi} \), and CSF volume) must be accompanied by an opposite change in the remaining intracranial volumes with a concomitant variation in ICP. This phenomenon is described through the intracranial storage capacity \( C_{ic} \). According to Marmarou et al. (28) and Avezaat et al. (4), an expression for the craniospinal capacity can be computed by assuming that the intracranial pressure-volume relationship is approximately monoexponential in type. We then have

\[
C_{ic} = \frac{1}{k_E \cdot P_{ic}}
\]

where \( k_E \) is the intracranial elastance coefficient as defined by Avezaat et al. (4). \( k_E \) is an index of the rigidity of the intracranial compartment; hence, it is inversely proportional to the pressure volume index (PVI) introduced by Marmarou et al. (28).

**Cerebrovascular Regulation Mechanisms**

Cerebrovascular regulation mechanisms work by modifying \( R_{pa} \) and \( C_{pa} \) (and hence blood volume) in the pial arterial-arteriolar vasculature. However, changes in these two parameters are not independent but are related through biomechanical and geometrical laws.

Two distinct control mechanisms are considered in this work, i.e., autoregulation and CO2 reactivity (see Fig. 2, top). The role of arterial oxygen is not included because \( O_2 \) pressure was maintained constant throughout the present trials.

As shown in the upper branch of Fig. 2, we assumed that autoregulation is activated by changes in CBF. Its action on the arterial-arteriolar pial vessels includes a static gain \( (G_{aut}) \) and first-order low-pass dynamics with the time constant \( \tau_{aut} \).

The lower branch in Fig. 2, top, represents CO2 reactivity. This includes a static gain as well \( (G_{CO2}) \) and first-order dynamics with the time constant \( \tau_{CO2} \). However, we used the logarithm of \( P_{a CO2} \) as input to the controller. The latter choice is justified because the response of pial vessels to \( CO_2 \) is correlated quite linearly with \( pH \) changes in the perivascular space. \( pH \) in turn, depends on the logarithm of \( CO_2 \) concentration via the Henderson-Hasselbalch equation. The minus sign in the upper branch signifies that an increase in CBF causes vasoconstriction, with a consequent decrease in pial vessel compliance and an increase in resistance. The dynamics of each mechanism are summarized through the low-pass frequency response shown in Fig. 2, bottom.

Finally, the two mechanisms do not superimpose linearly on pial vessels, but their interaction is characterized by significant nonlinearities (17, 56). To account for experimental and clinical evidences, we introduced two main nonlinearities. First, the strength of \( CO_2 \) reactivity in the model is not independent of the level of CBF but decreases significantly during severe ischemia (see Fig. 2, corrective factor \( A_{CO2} \)). In fact, severe ischemia is associated with tissue acidosis, which, in turn, buffers the effect of \( CO_2 \) changes on perivascular \( pH \). A second nonlinearity considers that the overall regulatory action is not the sum of the two mechanism actions but is instead passed through a sigmoidal static relationship with upper and lower saturation levels. The sigmoid accounts for the existence of maximal limits for the vascular response, i.e., total vasodilatation and maximal vasoconstriction.
Values were given to all model parameters under normal conditions to reproduce the intracranial hydro- and hemodynamics of a healthy subject. A list of all model parameters and their values under basal conditions can be found in Table 1. Details on the main parameter values can be found in previous papers (50, 53). A deeper comment on normal and pathological values for the six parameters individually estimated is provided in the DISCUSSION.

Figure 3 shows how the model can reproduce the regulatory mechanism actions in steady-state conditions with the use of basal values for the autoregulation and CO2 reactivity gains. Figure 3A shows the CBF percent changes vs. CPP during normocapnia, while Fig. 3B reports CBF percent changes vs. PaCO2 during normotension. In both cases, we can observe a satisfactory agreement between model results and physiological data.

MATERIALS AND METHODS

The model was used to reproduce the time pattern of ICP and VMCA in 13 neurosurgical patients during maneuvers that alter PaCO2 and mean SAP. We examined several tracings, obtained at different hours after head injury, in all patients. A total of 44 distinct tracings was thus simulated, each with a duration ranging between 12.5 and 93 min.

This study was approved by the local Ethics Committee, and informed consent of each subject’s next of kin was duly obtained.

Patients

The main characteristics of the patients are summarized in Table 2. All patients had severe head injuries (Glasgow coma scale < 8, mean age 30.5) typified by closed multifocal contusions or diffuse axonal injuries within the first few days after head trauma. After the removal of large epidural or subdural hematomas, where present, patients were put into intensive care and positioned supine with the head elevated 30° above the horizontal plane. They were sedated (midazolam and fentanyl) and paralyzed (vecuronium) at the time of the measurement. SAP (radial catheter), ICP (ventricular catheter), and end-tidal CO2 pressure (PetCO2) were monitored continuously. Jugular venous saturation in O2 (SvO2) was continuously monitored via a fiber-optic catheter (Opticath, 5.5 Fr; Abbott Laboratory) inserted retrogradely up to the jugular bulb of the dominant jugular vein. Moderate hyperventilation was induced to obtain a PetCO2 between 20 and 35 mmHg. According to the routine management proto-
Table 1. Basal values of model parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_a$</td>
<td>$2.38 \times 10^4$ mmHg·s·ml⁻¹</td>
</tr>
<tr>
<td>$R_{\text{CE}}$</td>
<td>$0.880$ mmHg·s·ml⁻¹</td>
</tr>
<tr>
<td>$k_{\text{m}}$</td>
<td>$0.155$ ml⁻¹</td>
</tr>
<tr>
<td>$P_{\text{CE}}$</td>
<td>$-2.5$ mmHg</td>
</tr>
<tr>
<td>$R_{\text{CE}}$</td>
<td>$0.366$ mmHg·s·ml⁻¹</td>
</tr>
<tr>
<td>$f_{\text{MCAn}}$</td>
<td>$0.14$ cm</td>
</tr>
<tr>
<td>$k_{\text{MCAn}}$</td>
<td>$12$</td>
</tr>
<tr>
<td>$R_{\text{CE}}$</td>
<td>$0.6$ mmHg·s·ml⁻¹</td>
</tr>
<tr>
<td>$V_{\text{mAn}}$</td>
<td>$13.5$ ml</td>
</tr>
<tr>
<td>$C_{\text{mAn}}$</td>
<td>$0.205$ mmHg/mmHg</td>
</tr>
<tr>
<td>$\Delta C_{\text{mAn}}$</td>
<td>$2.87$ ml/mmHg</td>
</tr>
<tr>
<td>$\Delta C_{\text{mAn}}$</td>
<td>$0.164$ mmHg</td>
</tr>
<tr>
<td>$k_{\text{mAn}}$</td>
<td>$13.1 \times 10^4$ mmHg³·s·ml⁻¹</td>
</tr>
<tr>
<td>$t_{\text{mAn}}$</td>
<td>$20$ s</td>
</tr>
<tr>
<td>$k_{\text{CO}_2}$</td>
<td>$15$</td>
</tr>
<tr>
<td>$b_{\text{CO}_2}$</td>
<td>$0.5$</td>
</tr>
<tr>
<td>$q_n$</td>
<td>$12.5$ ml/s</td>
</tr>
<tr>
<td>$P_{\text{va}}$</td>
<td>$6.0$ mmHg</td>
</tr>
</tbody>
</table>

**Basal values of estimated parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_a$</td>
<td>$526.3$ mmHg·s·ml⁻¹</td>
</tr>
<tr>
<td>$k_{\text{R}}$</td>
<td>$0.077$ ml⁻¹</td>
</tr>
<tr>
<td>$G_{\text{mAn}}$</td>
<td>$3.0$ ml·mmHg⁻¹·100% CBF change⁻¹</td>
</tr>
<tr>
<td>$t_{\text{CO}_2}$</td>
<td>$40$ s</td>
</tr>
<tr>
<td>$G_{\text{CO}_2}$</td>
<td>$8.0$</td>
</tr>
<tr>
<td>$P_{\text{aCO}_2}$</td>
<td>$40$ mmHg</td>
</tr>
</tbody>
</table>

Fixed model parameters were maintained throughout all simulations; values of other parameters were estimated through the best fitting procedure, $R_a$ and $R_{\text{CE}}$ cerebrospinal fluid (CSF) outflow and formation resistance; $R_{\text{pv}}$, proximal venous resistance; $k_{\text{mAn}}$ and $P_{\text{va}}$, constant parameters for intracranial venous compliance; $R_{\text{CE}}$, resistance of terminal intracranial veins during collapse; $k_{\text{EC}}$, elastance coefficient; $f_{\text{MCAn}}$, basal value of middle cerebral artery (MCA) radius; $k_{\text{MCAn}}$, constant parameter for MCA radius; $R_{\text{la}}$, large artery resistance; $V_{\text{mAn}}$ and $C_{\text{mAn}}$, basal pial arterial volume and compliance; $\Delta C_{\text{mAn}}$ and $\Delta C_{\text{mAn}}$, amplitude of sigmoidal curve; $k_{\text{mAn}}$, constant parameter for pial arterial resistance; $G_{\text{mAn}}$ and $G_{\text{CO}_2}$, time constant and gain of autoregulation; $t_{\text{CO}_2}$ and $G_{\text{CO}_2}$, time constant and gain of CO$_2$ reactivity; $k_{\text{CO}_2}$ and $b_{\text{CO}_2}$, constant parameters for CO$_2$ reactivity; $q_n$, basal cerebral blood flow; $P_{\text{va}}$, dural sinus pressure; $P_{\text{aCO}_2}$, set point for the CO$_2$ regulation mechanism.

Table 2. Clinical status of patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yr</th>
<th>GCS</th>
<th>Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>24</td>
<td>4</td>
<td>DAI</td>
</tr>
<tr>
<td>Ata</td>
<td>57</td>
<td>4</td>
<td>BSC</td>
</tr>
<tr>
<td>Bab</td>
<td>37</td>
<td>4</td>
<td>FC, SDH</td>
</tr>
<tr>
<td>Dbr</td>
<td>18</td>
<td>5</td>
<td>MFC</td>
</tr>
<tr>
<td>Deb</td>
<td>19</td>
<td>6</td>
<td>MFC, SAH, VI</td>
</tr>
<tr>
<td>Der</td>
<td>21</td>
<td>7</td>
<td>FC</td>
</tr>
<tr>
<td>Dug</td>
<td>16</td>
<td>4</td>
<td>BSC, VI</td>
</tr>
<tr>
<td>Gra</td>
<td>57</td>
<td>6</td>
<td>MFC, SDH, SAH</td>
</tr>
<tr>
<td>Hel</td>
<td>34</td>
<td>4</td>
<td>FC, SDH</td>
</tr>
<tr>
<td>Pro</td>
<td>24</td>
<td>3</td>
<td>MFC, SAH</td>
</tr>
<tr>
<td>Rum</td>
<td>19</td>
<td>5</td>
<td>MFC</td>
</tr>
<tr>
<td>Tho</td>
<td>37</td>
<td>6</td>
<td>FC, SDH</td>
</tr>
</tbody>
</table>

Mean age of patients was 30.5 yr. GCS, Glasgow coma scale at admission; MFC, multifocal contusion; FC, focal contusion; SDH, subdural hematoma; SAH, subarachnoid hemorrhage; BSC, brain stem contusion; VI, hemorrhagic ventricular inundation; DAI, diffuse axonal injury.

We performed CO$_2$ challenges at different levels of SAP. The studies were conducted as follows. After 30 min in a steady basal condition, patients were gradually hyperventilated by increasing respiratory frequency at constant tidal volume until VMCA no longer fell. During hyperventilation, jugular SV$_O_2$ was not allowed to drop below 50%. A short period of hyperventilation was then allowed by decreasing the respiratory rate. Hyperventilation was allowed up to a $P_{\text{aCO}_2}$ of $\approx 40$ mmHg or less if the ICP increased above 35 mmHg.

Ventilation was then adjusted to achieve the same $P_{\text{aCO}_2}$ obtained at the basal state. In a second session we kept $P_{\text{aCO}_2}$ constant and modulated norepinephrine perfusion to generate variations in SAP. When a new steady level of SAP was achieved, a second CO$_2$ challenge was performed. Quantitative details on the maneuvers (duration, $P_{\text{ETCO}_2}$, and mean SAP ranges) can be found in Table 3. Changes in $P_{\text{aCO}_2}$ always took a few minutes to be completed. Hence, our patients had received mannitol in the 6 h preceding the study. Before the study, when a steady-state hemodynamic condition was achieved, all patients underwent TCD measurement (Angiodyn DMS, 2-MHz probe) of both MCAs (1) to eliminate gross interhemispheric differences in the basal state. The probe was then secured in a special helmet in front of the temporal windows to continuously record $V_{\text{MCA}}$. The spectral outline of MCA Doppler time recording, SAP, ICP, and $P_{\text{ETCO}_2}$ signals were sampled at 200 Hz (digital-to-analog converter, National Instruments, Houston, TX, and a personal computer) and stored for off-line analysis. The signals were then numerically low-pass filtered (cut-off frequency 0.1 Hz), and a sample recorded every 4 s was stored again for comparison with model results.

Fig. 3. A: percent changes in CBF vs. mean systemic arterial pressure (SAP) evaluated with the model in steady-state conditions using a normal level of CO$_2$ arterial pressure ($P_{\text{aCO}_2} = 40$ mmHg). Throughout the simulations, intracranial pressure (ICP) was set at a constant level ($\approx 9.5$ mmHg). Model results (continuous line) are compared with the experimental data by Harper et al. (18) in rats (×) and MacKenzie et al. (26) in cats (○). B: percent changes of CBF vs. $P_{\text{aCO}_2}$ evaluated with the model in steady-state conditions at a normal level of mean SAP (100 mmHg). Model results (continuous line) are compared with the experimental data by Reivich (37) in monkeys (+) and Harper and Glass (17) in dogs (◆).
through a best fitting procedure. This consists of minimizing a suitable criterion function of the difference between in vivo data (in our case, ICP and \(V_{\text{MCA}}\)) and the corresponding model outputs, assuming that the model is stimulated by the same input perturbations used in the real trials. The general process of model identification is schematized in Fig. 4.

Unfortunately, the model contains too many parameters for them all to be individually estimated. Hence, when performing the best fitting procedure, we decided to estimate only the parameters that have the greater physiological and clinical meaning, i.e., those that summarize intracranial elasticity, CSF circulation, and cerebrovascular regulation. Hence, the parameters chosen are the CSF outflow resistance \(R_s\), the intracranial elastance coefficient \(k_E\), the gains of cerebral autoregulation \(G_{\text{aut}}\) and CO2 reactivity \(G_{\text{CO2-}}\), the time constant of the CO2 response \(\tau_{\text{CO2-}}\), and the position of the sigmoidal regulation curve. To this end, we individually estimated a “set point” for the CO2 regulation \(P_{\text{aCO2,0}}\) (see Eq. A15 in APPENDIX A). Changing the latter parameter is equivalent to shifting the normal working point along the sigmoidal regulation curve, that is, modifying the position of the upper and lower autoregulation limits. The latter choice is justified by the observation that the position of upper and lower limits for cerebrovascular regulation is affected by the patient’s metabolic need and by adaptation to gas level in the blood (32).

It is worth noting that the CSF production resistance \(R_p\) was not included in the previous list because, according to our earlier experience (52), this parameter is inversely correlated with CSF outflow resistance; hence, it cannot be estimated independently. Moreover, the time constant of autoregulation \(\tau_{\text{aut}}\) was not individually estimated because it is significantly smaller than the other time constants in the model and, hence, has only a minimal impact on the fitting process.

Automatic estimation of the aforementioned parameters was achieved by minimizing a least-square criterion function. To assess the accuracy of parameter estimates, we also evaluated the coefficient of variation (the percent standard deviation of the estimates) by using classic statistical techniques (5). A mathematical description of the criterion function and the equations for the assessment of the coefficient of variation are reported in APPENDIX B.

When the minimization procedure was performed, the initial values of model ICP and \(V_{\text{MCA}}\) were assigned on the basis of clinical data. In particular, the scaling factor \(k_v\) in Eq. 1 was computed separately in each trial to ensure that model \(V_{\text{MCA}}\) at the beginning of the simulation is the same as the first velocity data point.

The entire software program for mathematical computations was written using the scientific programming language Fortran 77 (AbSoft Fortran 77 for Windows) running on a Pentium-based personal computer. A user-friendly interface was also written in Visual Basic (Microsoft Visual Basic 5.0); the latter program permits handling of the parameter estimation procedure, visualization of parameter values, and graphic plotting in a simple and straightforward way.

RESULTS

The parameter values estimated in 44 tracings on 13 patients are reported in Table 4, together with the coefficient of variation of the estimates. To facilitate the analysis, all parameters in Table 4 (with the exception of \(P_{\text{aCO2,0}}\)) were normalized to the values in Table 1. The accuracy of the best fitting is summarized in two other columns of Table 4, in which the SD of the
residuals between the predicted and the actual measurements ($\Delta$ICP and $\Delta$VMCA) are presented. A column scatter graph showing these values in all 44 tracings is presented in Fig. 5. Figure 5 reveals that, in most cases, the SD of the residuals is of the same order as measurement accuracy ($\mu$1–2 mmHg for ICP, 4–5 cm/s for Doppler velocity), indicating that the model’s reproduction of clinical tracings is satisfactory. As for ICP, only four tracings exhibit residuals $\geq 3$ mmHg, denoting insufficient fitting, but three of these tracings refer to the same patient (patient Der). Velocity exhibits nine tracings in which residuals are $\geq 6$ cm/s, suggesting poor fitting. However, six of these are concerned with only two patients (patients All and Gra). These patients had high basal values of velocity (>100 cm/s), which might suggest the existence of either vasospasm or hyperemia and could explain the poor velocity fitting.

By looking at Table 4, one can observe that the estimated values of the parameter $P_{aCO_2,n}$ are significantly lower than normal. This result may reflect adaptation to the low level of PETCO$_2$ set before the maneuvers. To check this aspect, Fig. 6 shows the correlation between the basal PETCO$_2$ and the parameter $P_{aCO_2,n}$ for all 44 tracings. The correlation is high, apart from a few diverging points. However, three of these points refer to tracings (tracings Der4, Pra5, and Tho5) in which PCO$_2$ was maintained almost constant (see Table 3); hence, estimation of CO$_2$ reactivity parameters is scarcely significant. If these three points are excluded, correlation is as high as $r^2 = 0.86$.

Examples of the results of the best fitting procedure, obtained in two different patients, are shown in Figs. 7 and 8. The time pattern of the input quantities (i.e., mean SAP and $P_{aCO_2}$) are shown in Figs. 7 and 8, top, while a comparison between model outputs (ICP and VMCA) and the corresponding clinical data is shown in Figs. 7 and 8, bottom.

Figure 7 shows four different tracings obtained on the same day from patient Bab. The first two tracings contain only a CO$_2$ challenge, while arterial pressure was maintained constant. The third and fourth tracings comprise both SAP and $P_{aCO_2}$ maneuvers. It is clear from the first two tracings that a mild increase in CO$_2$ pressure, performed by starting from a baseline hypocapnic level (~20 mmHg), gave rise to a velocity increase and a significant ICP rise. Finally, even a modest decrease in $P_{aCO_2}$ was able to interrupt the uncontrolled increase in ICP, leading to rapid restoration of the baseline levels. The model is able to explain this chain of events with reliable values of its parameters (Table 4), ascribing the ICP time pattern to changes in cerebral blood volume.

The third and fourth tracings in Fig. 7 differ from the previous tracings because they comprise a hypertensive maneuver as well, and the CO$_2$ challenge occurs at a higher level of CPP. In the third tracing, a rapid increase in mean SAP causes a change in VMCA, so the patient is classified as having weak autoregulation ($\nu_{aut} = 0.47$, see Table 4). An index commonly used to estimate autoregulation in the clinical literature is the static autoregulation index (sARI) (30, 48), defined as the percentage changes in cerebrovascular resistance (CVR) divided by the percent changes in CPP. Values of sARI in normal subjects are $>0.85$ (see DISCUSSION). However, if this index is computed from the two arterial pressure maneuvers in the third clinical tracings of Fig. 5, one obtains the values $sARI = 0.47$ and $sARI = 0.39$, respectively, in accordance with model estimation of weak autoregulation.

By contrast, the increase of mean SAP in the fourth tracing in Fig. 7 does not evoke a clear velocity change, whereas it causes a moderate decrease in ICP, ascribed to active blood volume reduction. Hence, in this case the estimation procedure provides a high value for the normalized $\nu_{aut}$ (1.50, see Table 4). Accordingly, sARI

![Block diagram](http://ajpheart.physiology.org)
Table 4. Parameter values estimated in the 13 patients by automatic fitting procedure

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<th>Tracing</th>
<th>$R_o$</th>
<th>$k_g$</th>
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computed from the clinical tracing is as high as 0.89, which belongs within the range of normality.

An important aspect arising from the tracings in Fig. 7 is that the percent changes in TCD velocity per mmHg of CO2 change (\( \Delta V_{MCA}/\Delta P_{aCO2} \)), which is the index commonly used in the clinical literature to estimate CO2 reactivity, depend strongly on the level of CPP. Hence, this empirical index is not representative of the “true” CO2 reactivity. By contrast, the gain GCO2 in the model is quite independent of the CPP level. In fact, if the empirical index is computed in the first tracing, one obtains the value 1.84%/mmHg, while CPP decreases from 57 to 37 mmHg, i.e., below the autoregulation range. In the second tracing in Fig. 7, the same index is as low as 1.02%/mmHg, suggesting exhausted cerebrovascular regulation reserve, while CPP decreased during the maneuver to 34 mmHg. However, in the third tracing, the index is as high as +3.97%/mmHg. In fact, mean SAP was increased before the maneuver, and CPP always remained >66 mmHg, i.e., the overall maneuver was performed within the autoregulation range. Finally, in the fourth tracing in Fig. 7, we computed a value of \( \Delta V_{MCA}/\Delta P_{aCO2} = 2.94% / \text{mmHg} \), while CPP decreased from 84 to 61 mmHg. We can thus conclude that, when the CO2 challenge is performed at a higher CPP level (in the range of 60–80

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Fig. 5. Column scatter graph showing the standard deviations of the residuals (i.e., the last two columns in Table 4) for all 44 tracings examined. Horizontal lines represent the mean value of all residuals.
mmHg), the $V_{MCA}$ change per mmHg of $PaCO_2$ change is significantly higher compared with the case of low CPP (35–60 mmHg). Hence, the compensatory response to $CO_2$ is depressed by hypotension. It is worth noting that the model can explain this behavior, ascribing it to a nonlinear interaction between $CO_2$ reactivity and autoregulation (Fig. 2).

In some patients we performed several simultaneous $CO_2$ and SAP challenges in a single tracing, and we monitored the consequent ICP and $V_{MCA}$ changes over a long time period (40–90 min). Two tracings of this kind, monitored in patient Dug, are shown in Fig. 8. It is worth noting the capacity of the model to reproduce the consequences of several consecutive maneuvers at different SAP and $PaCO_2$ levels using just a single set of parameters. The dependence of the $CO_2$ reactivity index $\Delta V_{MCA}/\Delta PaCO_2$ on CPP is evident by comparing the results of the two consecutive $CO_2$ challenges in the first tracing in Fig. 8. In the first maneuver, performed at a CPP always >72 mmHg (i.e., within the autoregulation range), we computed a $\Delta V_{MCA}/\Delta PaCO_2 = 4.11%/\text{mmHg}$, which is quite normal. By contrast, the second $CO_2$ maneuver provides an index $\Delta V_{MCA}/\Delta PaCO_2$ as low as 2.13%/mmHg, while CPP decreased from 57.4 to 50 mmHg, approaching the autoregulation lower limit. Accordingly, the model estimates that

Fig. 7. Results of the estimation procedures performed on 4 different tracings measured a few hours apart in patient Bab. For each tracing, the upper panel represents the manipulated quantities for mean SAP (top) and $PaCO_2$ (bottom) used as input to the model, while the lower panel shows a comparison between model and in vivo $V_{MCA}$ (top) and ICP (bottom). Open circles connected with a thin line represent in vivo data, while thick lines are model simulation results obtained with the estimation algorithm. For each tracing, parameters were estimated again. The resulting parameter estimates are reported in Table 4.
G_{CO_2} is quite normal in this patient (normalized value 0.93) and ascribes the apparent reduction in CO_2 reactivity of the second maneuver to the attainment of maximal vasodilation at low CPP. In tracing Dug2, the CO_2 maneuver is performed at normal CPP (always >74 mmHg), the index ΔV_{MCA}%/ΔP_{aCO_2} = 4.55%/mmHg, and estimated CO_2 reactivity in the model is rather normal.

Finally, the sARI computed during the arterial pressure maneuvers in the two tracings of Fig. 8 is 0.42 and 0.69, respectively, denoting a weak autoregulation. Accordingly, the model provides a G_{aut} lower than normal (normalized values close to 0.6).

**DISCUSSION**

The present work was designed with two main purposes: to find a reliable quantitative description of the main hemodynamic changes occurring in head-injured patients during SAP and CO_2 pressure challenges, and to verify the possibility of characterizing intracranial dynamics in each patient through a limited number of parameters. Before the significance and limitations of the obtained results are examined, it is important to provide a critical analysis of both the measurement technique employed and the quality of clinical data available.

A first important problem concerns the use of the TCD technique to achieve dynamic information on CBF percent changes. This choice is acceptable because previous studies in head-injured patients demonstrated the existence of a good proportionality, with a slope close to 1, between percent variations in TCD velocity and CBF estimated with the Fick principle. However, in patients with elevated V_{MCA} >100 cm/s, the slope was not strictly close to 1, and TCD variations underestimated CBF variations (47). This result is probably due to the fact that hyperemia or vasospasm is associated with modifications in velocity profile and/or interhemispheric heterogeneity of vascular reactivity. This problem may have caused some of the high differences (>6–7 cm/s) between model predictions and clinical data observed in a few patients (especially patients Gra and All) who had elevated blood flow velocity.

A second problem is that we measured end-tidal CO_2 during the clinical trials, whereas arterial CO_2 is the true stimulus for cerebrovascular regulation. We are aware that in some head-injured patients the gradient between end-tidal and arterial PCO_2 can be increased as a consequence of neurogenic pulmonary edema, which increases ventilation perfusion inhomogeneity. However, none of the patients analyzed exhibited symptoms of pulmonary edema or had pulmonary disease.

A final problem is that SAP was modified with norepinephrine. In the present simulations we assumed that infusion of norepinephrine does not modify the diameter of the insonated vessel or change cerebrovascular reactivity. This assertion is speculative, but it is supported by data from Olesen (33). This author observed that intracarotid application of adrenalin or norepinephrine does not affect regional cerebral blood flow in humans, and these drugs do not alter the diameter of large intracranial arteries, as shown by angiography. This result can explain why similar V_{MCA} variations were observed during autoregulatory tests realized by means of pharmacological infusion of norepinephrine and by means of nonpharmacological methods (44, 48).

In most tracings examined, the model was able to show rather good reproduction of the observed ICP and V_{MCA} time patterns, with a standard error of the residuals of the same order as measurement errors. Moreover, the capacity of the present model to reproduce ICP and velocity tracings is equivalent to that of
the previous, more complex model (25) but with much shorter computation time. However, it is important to emphasize that reproduction of real tracings was not achieved a priori, based on knowledge of a patient’s condition, but only a posteriori through a best fitting procedure. In other words, the present simplified model needs to be used together with a fitting procedure to assign some parameter values.

Among the estimated parameters, two are of particular interest because they contribute to intracranial hypertension and clinical status in patients with severe head injury; i.e., intracranial elastance and CSF outflow resistance. Clinicians are strongly interested in a quantitative knowledge of these parameters because their alterations require therapeutic intervention before the occurrence of secondary brain damage. However, the methods presently available to estimate these parameters often provide contradictory results (24, 27) and are not without criticism (15, 16). As a consequence, no gold standard method to derive these parameters is yet at hand.

Furthermore, knowledge of the autoregulation and CO2 reactivity gains could also be important in clinical practice to choose the correct management and to distinguish between the patients who need sustained elevated CPP and those who need hyperventilation (9, 39). Estimation of the strength of regulation mechanisms, however, as obtained by classic indexes (such as CBF percent change or resistance changes per mmHg), is misleading because, as in the example of Figs. 7 and 8, this may depend on CPP, ICP changes, and the working point along the regulation characteristic.

In the present study, parameters have been estimated by using a classic identification schema (Fig. 4), i.e., by minimizing the square of residuals between clinical data and model results. A crucial problem is whether the obtained parameter values have a reliable meaning or are merely the result of curve fitting. This problem will be critically examined below for each estimated parameter.

**CSF Outflow Resistance**

The values of the CSF outflow resistance ($R_o$) reported in the clinical literature differ significantly among authors, depending on the specific technique used to derive this parameter. In general, the bolus injection technique provides values of $R_o$ three or four times smaller than the values obtained with the steady-state methods (42, 45). Basically, values of $R_o$ evaluated with steady-state techniques in subjects with normal CSF circulation range between 4.4 and 15.6 mmHg min/ml (normalized values 0.5–1.78, with reference to our basal value reported in Table 1) (12, 29). These values are supported by those measured by Cutler et al. (10) based on isotope clearance in 11 patients ($R_o$ value of 9.7 ± 1.0).

Values of $R_o$, measured in patients with severe head injury with stationary withdrawal (24) show a significant increase compared with normal values, ranging between 21 and 85 mmHg·min/ml (normalized range 2.4–9.7). By contrast, lower values of $R_o$ were obtained by Marmarou et al. (27) in the severe head injury with the bolus technique (3.15–36.62 mmHg·min/ml; normalized range 0.4–4.17).

The values of $R_o$ estimated in the present study show a good agreement with those measured by Kosteljanetz (24). In 12 of 13 patients, $R_o$ appears significantly increased compared with the basal value (normalized range 2.0–9.0). This result supports the idea that impairment in CSF outflow may represent a major contribution to intracranial hypertension in severe head injury.

**Intracranial Elastance Coefficient**

Normal values for $k_E$, computed by means of bolus tests, lie in the range 0.076–0.108 ml⁻¹ (normalized range 1.0–1.4) (43). Values >0.128 ml⁻¹ (normalized value 1.66) are generally considered abnormal and indicative of a decreased intracranial storage capacity. Values in patients with severe head injury were measured by Kosteljanetz (24). $k_E$ ranged between 0.08 and 0.76 ml⁻¹ (normalized range 1.05–10.0). Values of $k_E$ during bolus tests were estimated by Ursino et al. (55) in head-injured patients by using a simple model of intracranial dynamics. The values (normalized at the basal value shown in Table 1) extended between 0.63 and 3.22.

Normalized values of $k_E$ estimated in this study range between 0.7 and 2.9, i.e., we observed both patients with normal elastance and patients with a significant increase in $k_E$, suggesting a reduction in the intracranial storage capacity. On average, the elastance coefficient is increased in head injury compared with normality. This result agrees with the observation by Kosteljanetz (24) and our previous observation with the bolus technique (55).

**Autoregulation Gain**

In normal subjects, sARI, which is defined as the percentage change in CVR per percent change in CPP (i.e., $sARI = \Delta CVR/%\Delta CPP$), ranges between 0.85 and 0.95 (30, 44, 48). In our model, similar values of sARI can be obtained during normocapnia by changing $G_{aut}$ (normalized) between 1.0 and 5.0. This can be assumed to be a normal autoregulation range in our model.

Autoregulation is known to be significantly impaired by many cerebral diseases, including head injury. Results from Bouma and Muizelaar (6) and Matta et al. (30) suggest that patients with head injury can be discriminated in three classes: normal autoregulation ($sARI > 0.85$), moderately impaired autoregulation ($0.85 > sARI > 0.5$), and severely impaired autoregulation ($0.5 > sARI$). According to our simulations, the values of $G_{aut}$ parameters (normalized) that discriminate between these three classes are $G_{aut} > 1.0$ (normal), $0.5 < G_{aut} < 1$ (moderately impaired), and $G_{aut} < 0.5$ (strongly impaired).
The values of $G_{\text{aut}}$ estimated in this study range between 0.2 (impaired autoregulation) and 1.5 (normal autoregulation) in accordance with the literature.

$\text{CO}_2$ Reactivity

An index for $\text{CO}_2$ reactivity frequently used in the clinical literature is the percent CBF change (or percentage velocity change) per $\text{PaCO}_2$ change (in mmHg). Normal values (22, 34) are approximately as great as 4–4.5 CBF%/mmHg with an SD as great as ±1 CBF%/mmHg. This range of normal $\text{CO}_2$ reactivity is covered in the model when $G_{\text{CO}_2}$ is varied between 1.0 and 4.0.

$\text{CO}_2$ reactivity may decrease below 2 CBF%/mmHg in some patients with severe head injury, although in other patients $\text{CO}_2$ reactivity is preserved despite the trauma. Data in Tenjin et al. (46) suggest that the value 2 CBF%/mmHg may be considered as a threshold to discriminate between patients with preserved and impaired $\text{CO}_2$ reactivity. According to our simulations, this threshold corresponds to a value of normalized $G_{\text{CO}_2}$ approximately as low as 0.66.

In this work we estimated values of normalized $G_{\text{CO}_2}$ ranging between 0.21 and 2.32 (average 0.85). This range agrees with values reported in the clinical literature and confirms the existence of patients with preserved $\text{CO}_2$ reactivity as well as patients with almost absent $\text{CO}_2$ response.

The parameter $\tau_{\text{CO}_2}$, estimated in the present trials, ranges between normal and threefold normal values (i.e., 2 min). These high values might depend on the impairment of some feedback mechanisms in head-injured patients or may reflect a high time delay between changes in $\text{PETCO}_2$ and changes in pH at cerebral arterioles.

Finally, the set point $\text{PaCO}_2$, is significantly lower than normal in most patients. We think that these low values should not be ascribed to the traumatic pathology but, rather, that they represent adaptation to the low $\text{PCO}_2$ level set in the patients before the maneuvers, probably due to a reset of CSF pH to normal values after prolonged hyperventilation (41). This assumption is strongly supported by the high correlation between $\text{PaCO}_2$ and $\text{PETCO}_2$, shown in Fig. 6.

The previous analysis confirms that parameter estimates belong within the range reported in the clinical literature for patients with severe head injury. This observation suggests the possibility that the present method may be of clinical value to assess pathological alterations in intracranial dynamics. An important problem, however, concerns the accuracy by which parameters can be estimated from the clinical tracings and the uniqueness of the obtained solutions. Contradictory conclusions can be drawn on the basis of this major point. In favor of the accuracy of the estimates, we can observe that, in several cases, parameter estimation achieved in the same patient using tracings recorded a few hours apart furnished very similar results (compare tracings All4 vs. All5, Bab1 vs. Bab2, Dbr1 vs. Dbr2, Dug1 vs. Dug2, Hel1 vs. Hel2, and Tho1 vs. Tho2). The repeatability of parameter estimates is especially satisfactory when the clinical maneuvers comprise both $\text{CO}_2$ and SAP challenges performed at different times in the same tracing (as in Fig. 8). In a few other cases, however, parameters exhibited large fluctuations when passing from one trial to the next. This intrinsic variability might depend on an effective change in a patient’s intracranial status but might also be caused by insufficient accuracy in parameter estimates. At present we have not enough elements to discriminate between these two possibilities, but a few arguments can be developed.

First, we can observe that, in most cases, the variability in the estimates of the CSF outflow resistance within the same patient is small enough to permit discrimination among patients with normal CSF outflow (normalized $R_o = 1–2$), moderate elevation in $R_o$ ($\sim 2.5–5$), or large elevation in $R_o$ ($\sim 6–9$). Similarly, values of $k_E$ maintain certain coherence within the same patient. In most cases, estimation of $k_E$ remains rather constant or decreases during the treatment, suggesting an improvement in intracranial elasticity. The remarkable case of patient Rum will be examined below.

By contrast, the autoregulation gain, as well as the gain and time constant of $\text{CO}_2$ reactivity, exhibits a wide dispersion, which is evident not only from one patient to the next but also within the same patient. We think that the reason for this variability may be the significant correlation existing among these parameters, which often precludes the possibility of their accurate unequivocal estimation. To attenuate this problem, it would be important to use tracings in which SAP and $\text{CO}_2$ challenges are performed separately (such as tracings in Fig. 8); multiple information, in fact, may provide more accurate estimation of correlated parameters.

A final important issue is that the estimated parameter values should have some relationship with the patient’s clinical status to effectively support the clinical practice. Naturally, clinical validation of the model is well beyond the limits of the present work and should be the subjects of future, more clinically oriented studies. However, patient Rum represents an exemplary case. This patient developed a secondary compressive chronic subdural hematoma during the recovery. Surgical evacuation was performed at the 16th day after trauma (i.e., between tracings Rum2 and Rum3). It is interesting to observe that the estimation procedure predicts an increase in $R_o$ and a strong increase in $k_E$ (indicating reduced intracranial elasticity) at days 15 and 16 before the surgical procedure. However, these parameters returned rather close to normal after surgical evacuation (Table 4).

APPENDIX A

All model equations are presented in APPENDIX A. Parameters used in the estimation algorithm are as follows: $R_o$ in Eq. A3, $k_E$ in Eq. A4, $G_{\text{aut}}$ in Eq. A14, and $G_{\text{CO}_2}$, $\tau_{\text{CO}_2}$, and $\text{PaCO}_2$ in Eq. A15.
Intracranial Hemodynamics and Hydrodynamics

Model equations for intracranial dynamics are written by imposing the mass preservation at all nodes in Fig. 1.

Application of mass preservation at the intracranial storage capacity, $C_{in}$, leads to the following differential equation

$$C_{in} \frac{dP_{in}}{dt} = \frac{dV_{pa}}{dt} + \frac{dV_{vi}}{dt} + q_t - q_o \quad (A1)$$

where $V_{pa}$ and $V_{vi}$ are blood volume at the pial arterial-arteriolar and venous vascular beds, respectively, $P_{in}$ is intracranial pressure, and $q_t$ and $q_o$ are the rates of CSF formation at cerebral capillaries and CSF outflow at the dural sinuses, respectively. Because both processes are assumed to be passive and unidirectional, we can write

$$q_t = \begin{cases} \frac{P_s - P_{pa}}{R_s} & \text{if } P_s > P_{pa} \\ 0 & \text{otherwise} \end{cases} \quad (A2)$$
$$q_o = \begin{cases} \frac{P_{in} - P_{vn}}{R_{vn}} & \text{if } P_{in} > P_{vn} \\ 0 & \text{otherwise} \end{cases} \quad (A3)$$

where $R_s$ and $R_{vn}$ are the resistances to CSF formation and CSF outflow, respectively, $P_{pa}$ is cerebral capillary pressure, and $P_{vn}$ is dural sinus pressure.

Intracranial storage capacity is inversely proportional to ICP, which implies a monoexponential pressure-volume relationship. Hence

$$C_{in} = \frac{1}{k_E \cdot P_{in}} \quad (A4)$$

where $k_E$ is the intracranial elastance coefficient.

Mass preservation at node $pa$ gives us the following differential equation

$$\frac{dV_{pa}}{dt} = \frac{P_a - P_{pa}}{R_{la} + (R_{pa}/2)} - \frac{P_{pa} - P_{c}}{R_{pa}/2} \quad (A5)$$

where $P_a$ is systemic arterial pressure, $P_{pa}$ is pial arterial pressure, and $R_{la}$ and $R_{pa}$ are the hydraulic resistances of the basal intracranial arteries and the pial arterial-arteriolar vascular bed, respectively.

An expression for capillary pressure can be obtained by writing mass preservation at node $c$. We have

$$\frac{P_{pa} - P_{c}}{R_{pa}/2} = q_t + \frac{P_{in} - P_t}{R_{pv}} \quad (A6)$$

where $P_t$ is the cerebral venous pressure and $R_{pv}$ is the hydraulic resistance of the proximal intracranial veins. By rearranging Eq. A6 and taking Eq. A2 into account, we can easily write capillary pressure as a function of the other state variables in the model (i.e., $P_{pa}$, $P_{in}$, and $P_t$).

Furthermore, by imposing mass preservation at the cerebral veins (node $vi$), a further differential equation is obtained

$$\frac{dV_{vi}}{dt} = \frac{P_c - P_v}{R_{pv}} - \frac{P_v - P_{vs}}{R_{vs}} \quad (A7)$$

where $R_{vs}$ represents the resistance of the terminal intracranial veins. An expression for this quantity has been computed as a function of ICP, cerebral venous pressure, and venous sinus pressure, assuming that the terminal veins behave as a Starling resistor (50). We have

$$R_{vs} = \frac{P_{vn} - P_{vs}}{P_v - P_{ic}} \quad (A8)$$

where $R_{vs}$ represents the terminal vein resistance when $P_{vn} = P_{vs}$.

To complete the model, we need expressions for blood volume changes in the pial arterial-arteriolar and venous vascular beds (i.e., $dV_{pa}/dt$ and $dV_{pa}/dt$) to be used in Eqs. A1, A5, and A7.

Because cerebral veins behave passively, their blood volume variations can only be ascribed to changes in transmural pressure. Hence

$$\frac{dV_{vi}}{dt} = C_{vi} \left( \frac{dP_v}{dt} - \frac{dP_{ic}}{dt} \right) \quad (A9)$$

in which intracranial venous compliance, $C_{vi}$, is computed by assuming a monoexponential pressure-volume relationship for cerebral veins. Hence

$$C_{vi} = \frac{k_{ven}}{(P_v - P_{ic} - P_{vs})} \quad (A9')$$

where $k_{ven}$ is a constant parameter and $P_{vs}$ represents the transmural pressure value at which cerebral veins collapse.

By contrast, blood volume changes in the arterial-arteriolar pial vascular bed can be ascribed to both transmural pressure changes and the action of cerebrovascular control mechanisms. In particular, as shown in the block diagram of Fig. 2, control mechanisms dynamically modify the compliance $C_{pa}$. Hence

$$\frac{dV_{pa}}{dt} = C_{pa} \left( \frac{dP_{pa}}{dt} - \frac{dP_{ic}}{dt} \right) + \frac{dC_{pa}}{dt} \left( P_{pa} - P_{pa} \right) \quad (A10)$$

The first term in the right-hand member of Eq. A10 represents passive blood volume changes, imputable to transmural pressure alterations, whereas the second term accounts for active volume changes consequent to the action of cerebrovascular control mechanisms.

Finally, the model permits computation of CBF, $q$, and blood velocity at the middle cerebral artery ($V_{MCA}$). From the mechanical analogy of Fig. 1, the following expression for CBF at the tissue level is derived

$$q = \frac{P_{pa} - P_{c}}{R_{pa}/2} \quad (A11)$$

An expression for $V_{MCA}$ is obtained by computing the ratio of blood flow in the MCA to cross-sectional area. To this end, we assumed that about one-third of CBF in the first segment of Fig. 1 courses across each MCA. Hence

$$V_{MCA} = \frac{1}{3} \left( \frac{P_a - P_{pa}}{R_{la} + (R_{pa}/2)} \right) \left( \frac{1}{\pi \cdot r_{MCA}^2} \right) \quad (A12)$$

where $r_{MCA}$ denotes the MCA inner radius. Because basal intracranial arteries behave passively, inner radius is calculated from transmural pressure ($P_{pa} - P_{ic}$), using a monoclex-
ponential pressure-radius curve taken from Hayashi et al. (19). We can write

$$r_{\text{MCA}} = r_{\text{MCA}_0} \frac{1}{k_{\text{MCA}}} \ln \left( \frac{P_a - P_{ic}}{P_{an} - P_{ic}} \right) + 1$$  (A13)

where $k_{\text{MCA}}$ is a constant parameter representing the rigidity of the artery, and the subscript n denotes a quantity in basal condition.

### Cerebrovascular Control Mechanisms

The model assumes that cerebrovascular control mechanisms modify the pial arterial-arteriolar compliance, $C_{pa}$, and resistance, $R_{pa}$, according to the block diagram of Fig. 2. The actions of autoregulation and CO$_2$ reactivity are individually described by means of first-order low-pass dynamics, with time constants $\tau_{\text{aut}}$ and $\tau_{\text{CO}_2}$ and gains $G_{\text{aut}}$ and $G_{\text{CO}_2}$, respectively. This corresponds to writing the following differential equations

$$\tau_{\text{aut}} \cdot \frac{dx_{\text{aut}}}{dt} = -x_{\text{aut}} + G_{\text{aut}} \left( \frac{q - q_n}{q_n} \right)$$  (A14)

$$\tau_{\text{CO}_2} \cdot \frac{dx_{\text{CO}_2}}{dt} = -x_{\text{CO}_2} + G_{\text{CO}_2} \cdot A_{\text{CO}_2} \cdot \log_{10} \left( \frac{P_{a\text{CO}_2}}{P_{a\text{CO}_2,n}} \right)$$  (A15)

where $x_{\text{aut}}$ and $x_{\text{CO}_2}$ are two state variables of the model that account for the effect of autoregulation and CO$_2$ reactivity, respectively, and $q_n$ and $P_{a\text{CO}_2,n}$ are set points for the regulatory mechanisms. In writing Eq. A14 we assumed that autoregulation is sensitive to CBF relative changes, whereas CO$_2$ reactivity in Eq. A15 depends on the logarithm of CO$_2$ pressure. The latter choice has been adopted to emphasize that the response of cerebral vessels to CO$_2$ is correlated quite linearly with pH in the perivascular space. Furthermore, the strength of CO$_2$ reactivity in the model is not constant but decreases drastically during severe ischemia. This phenomenon is reproduced through a corrective factor ($A_{\text{CO}_2}$) in Eq. A15. We used the following expression for the dependence of $A_{\text{CO}_2}$ on CBF

$$A_{\text{CO}_2} = \frac{1}{1 + \exp\left[-k_{\text{CO}_2}(q - q_n)/q_n - b_{\text{CO}_2}\right]}$$  (A16)

where $k_{\text{CO}_2}$ and $b_{\text{CO}_2}$ are constant parameters. The values of these parameters were set so that $A_{\text{CO}_2}$ remains close to 1 until CBF is approximately &gt;50% of $q_n$ and then exponentially decreases (see Fig. 2, inset).

Finally, the two control actions $x_{\text{aut}}$ and $x_{\text{CO}_2}$ are not simply summed up to provide a value for pial artery compliance but are passed through a sigmoidal relationship with upper and lower saturation levels. Hence

$$C_{\text{pa}} = \frac{(C_{\text{pa}_n} - \Delta C_{\text{pa}}/2) + (C_{\text{pa}_n} + \Delta C_{\text{pa}}/2) \cdot \exp\left[(x_{\text{CO}_2} - x_{\text{aut}})/k_{\text{C}_2}\right]}{1 + \exp\left[(x_{\text{CO}_2} - x_{\text{aut}})/k_{\text{C}_2}\right]}$$  (A17)

where $k_{\text{C}_2}$ is a constant parameter, inversely proportional to the central slope of the sigmoidal curve, and $C_{\text{pa}_n}$ and $\Delta C_{\text{pa}}$ are the central value and the amplitude of the sigmoidal curve. According to Eq. A17, the decrease in CBF and the increase in CO$_2$ pressure cause vasodilation with an increase in compliance; by contrast, any CBF increase or CO$_2$ pressure decrease causes vasoconstriction associated with compliance reduction.

A value for the constant parameter $k_{\text{C}_2}$ in Eq. A17 was given to set the central slope of the sigmoidal curve to $+1$. This is obtained by assuming $k_{\text{C}_2} = \Delta C_{\text{pa}}/4$. With this choice, $G_{\text{aut}}$ and $G_{\text{CO}_2}$ in Eqs. A14 and A15 represent the central gains of the two mechanisms.

However, the sigmoidal curve is not symmetrical because, according to the literature (23, 31), the increase in blood volume induced by vasodilation is higher than the blood volume decrease induced by vasoconstriction. Hence, two different values must be chosen for the parameter $\Delta C_{\text{pa}}$ in Eq. A17, depending on whether vasodilation or vasoconstriction is considered. We have

$$\begin{align*}
\text{if } x_{\text{CO}_2} - x_{\text{aut}} &gt; 0 \text{ then } \Delta C_{\text{pa}} = \Delta C_{\text{pa}_1}/4; & k_{\text{C}_2} = \Delta C_{\text{pa}_1}/4 \\
\text{if } x_{\text{CO}_2} - x_{\text{aut}} &lt; 0 \text{ then } \Delta C_{\text{pa}} = \Delta C_{\text{pa}_2}; & k_{\text{C}_2} = \Delta C_{\text{pa}_2}/4
\end{align*}$$  (A18)

As a result of Eqs. A17 and A18, the upper and lower saturation levels of the sigmoidal curve are $C_{\text{pa}_n} + \Delta C_{\text{pa}_1}/2$ and $C_{\text{pa}_n} - \Delta C_{\text{pa}_2}/2$, respectively.

An expression for $dC_{\text{pa}}/dt$ in Eq. A10 is obtained by differentiating Eq. A17 to

$$\frac{dC_{\text{pa}}}{dt} = \frac{\Delta C_{\text{pa}}}{k_{\text{C}_2}} \cdot \frac{\exp[(x_{\text{CO}_2} - x_{\text{aut}})/k_{\text{C}_2}]}{[1 + \exp[(x_{\text{CO}_2} - x_{\text{aut}})/k_{\text{C}_2}]]^2} \times \frac{d(x_{\text{CO}_2} - x_{\text{aut}})}{dt}$$  (A19)

Finally, the action of cerebrovascular control mechanisms affects the hydraulic pial artery resistance, $R_{pa}$, as well. Because blood volume, as a first approximation, is directly proportional to the inner radius second power, while resistance is inversely proportional to inner radius forth power, the following relationship holds between pial artery volume and resistance

$$R_{\text{pa}} = \frac{k_{R} \cdot C_{\text{pa}}^2}{V_{\text{pa}}}$$  (A20)

where $k_{R}$ is a constant parameter. The square value of $C_{\text{pa}}$ has been included in the numerator of Eq. A20 to make hydraulic resistance in basal conditions independent of blood volume; i.e., only the changes in $R_{\text{pa}}$ and $C_{\text{pa}}$ are related through Eq. A20.

### APPENDIX B

Estimation of model parameters was carried out by means of an automatic procedure. Starting from an initial guess, certain model parameters were modified iteratively by a numerical algorithm to minimize a cost function of the difference between model and in vivo results (Fig. 4). Because statistical information on the measurement errors was not available, we adopted a weighted least-square cost function (5), that is

$$F(\theta) = W_{\text{ICP}} \cdot \sum_{i=1}^{N} \left( P_{\text{ic}_{\text{m}}}^i(t_i) - P_{\text{ic}i}^i(t_i), P_{\text{ETCO}_2}(t_i), \Theta) \right)^2 + W_{\text{MCA}} \sum_{i=1}^{N} \left( V_{\text{MCA}_{\text{m}}}^i(t_i) - V_{\text{MCA}i}^i(t_i), P_{\text{ic}}(t_i), P_{\text{ETCO}_2}(t_i), \Theta) \right)^2$$  (A21)

where $P_{\text{ic}i}^i(t)$ and $V_{\text{MCA}_{\text{m}}}^i(t)$ represent the in vivo ICP and $V_{\text{MCA}}$ values at the instant $t_i$, $P_{\text{ic}i}^i(t)$ and $V_{\text{MCA}_{\text{m}}}^i(t)$ are the corresponding model predictions at the same instant, $P_{\text{ic}}$ and $P_{\text{ETCO}_2}$ are systemic arterial pressure and end-tidal CO$_2$ tension (to be used as inputs for the model), $N$ is the number of available data points, $W_{\text{ICP}}$ and $W_{\text{MCA}}$ are weighting factors, and $\theta =$
The sensitivity matrix $S(\hat{\theta})$ is the $2N \times p$ sensitivity matrix that contains the derivatives of model outputs at the instants of observation $t_i$, computed with respect to each of the $p$ estimated parameters; $W$ is the $2N \times 2N$ diagonal matrix of weights, that is

$$W = \text{diag}(W_{\text{ICP}}, \ldots, W_{\text{ICP}}, W_{\text{MCA}}, \ldots, W_{\text{MCA}})$$

and $U$ is a $2N \times 2N$ diagonal matrix that contains estimates of the error variance for the two outputs, that is

$$U = \text{diag}(\sigma_{\text{ICP}}^2, \ldots, \sigma_{\text{ICP}}^2, \sigma_{\text{MCA}}^2, \ldots, \sigma_{\text{MCA}}^2)$$

where the variance of the ICP measurements is estimated as follows

$$\sigma_{\text{ICP}}^2 = \frac{W_{\text{ICP}}}{N - p/2}$$

$$\times \sum_{i=1}^{N} (P_{\text{ICP}}^{(i)}(t_i) - P_{\text{ICP}}^{(i)}[t_i, P_{\text{MCA}}^{(i)}(t_i), P_{\text{ETCO}_2}^{(i)}(t_i), \hat{\theta}])^2$$

and the variance of the $V_{\text{MCA}}$ measurements is

$$\sigma_{\text{MCA}}^2 = \frac{W_{\text{MCA}}}{N - p/2} \cdot \sum_{i=1}^{N} (V_{\text{MCA}}^{(i)}(t_i) - V_{\text{MCA}}^{(i)}[t_i, P_{\text{MCA}}^{(i)}(t_i), P_{\text{ETCO}_2}^{(i)}(t_i), \hat{\theta}])^2$$

The sensitivity matrix $S(\hat{\theta})$ was computed by using a forward approximation for the derivatives.

Finally, starting from knowledge of the covariance matrix, the accuracy in the estimation of the $i$th parameter, $\hat{\theta}_i$, was evaluated by computing the coefficient of variation of the estimate, $\text{CV}_i$,

$$\text{CV}_i = \frac{v_{\theta_i}(\hat{\theta})}{\hat{\theta}_i} \cdot 100$$

where $v_{\theta_i}(\hat{\theta})$ denotes the $i$th diagonal element of the covariance matrix, that is, the variance of the $i$th estimate.

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