Intracranial pressure dynamics in patients with acute brain damage

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Intracranial pressure dynamics in patients with acute brain damage. J. Appl. Physiol. 82(4): 1270–1282, 1997.—The time pattern of intracranial pressure (ICP) during pressure-volume index (PVI) tests was analyzed in 20 patients with severe acute brain damage by means of a simple mathematical model. In most cases, a satisfactory fitting between model response and patient data was achieved by adjusting only four parameters: the cerebrospinal fluid (CSF) outflow resistance, the intracranial elastance coefficient, and the gain and time constant of cerebral autoregulation. The correlation between the parameter estimates was also analyzed to elucidate the main mechanisms responsible for ICP changes in each patient. Starting from information on the estimated parameter values and their correlation, the patients were classified into two main classes: those with weak autoregulation (8 of 20 patients) and those with strong autoregulation (12 of 20 patients). In the first group of patients, ICP mainly reflects CSF circulation and passive cerebral blood volume changes. In the second group, ICP exhibits paradoxical responses attributable to active changes in cerebral blood volume. Moreover, in two patients of the second group, the time constant of autoregulation is significantly increased (>40 s). The correlation between the parameter estimates was significantly different in the two groups of patients, suggesting the existence of different mechanisms responsible for ICP changes. Moreover, analysis of the correlation between the parameter estimates might give information on the directions of parameter changes that have a greater impact on ICP.

intracranial dynamics; pressure-volume index tests; cerebral autoregulation; mathematical modeling

Pressure-volume index (PVI) tests are frequently used in neurosurgical intensive care units to derive information on intracranial pressure (ICP) dynamics in patients with severe brain damage. For these tests a small amount of fluid (1–4 ml) is injected into or withdrawn from the cranial cavity and the consequent ICP time pattern is monitored. The basic assumption is that the immediate ICP response to a volume load provides information on the pressure-volume characteristic of the craniospinal compartment (hence, on the intracranial storage capacity), whereas the subsequent ICP trend also reflects the status of the cerebrospinal fluid (CSF) circulatory pathways.

Several authors, however, recently questioned this approach (4, 12, 13), suggesting that the ICP time pattern during PVI tests may also contain information on cerebral hemodynamics and on the status of cerebrovascular autoregulation mechanisms. The rationale of this idea is that, after bolus injection or withdrawal, cerebral blood volume (CBV) may vary significantly, and these variations superimpose themselves on those caused by the initial volume load and by the subsequent CSF circulation. Hence, analysis of PVI tests may lead to a misleading interpretation of intracranial dynamics, if autoregulation mechanisms and the status of cerebral vessels are not properly taken into account.

In practice, analysis of the ICP response to bolus injection or bolus withdrawal requires use of a mathematical model including the main parameters of craniospinal system dynamics. The value of these parameters is then individually estimated by looking for a best fit between model predictions and the actual patient’s ICP tracings. In the classic model of Marmarou et al. (18, 19), the best fit can be achieved by using simple analytic equations, which justifies the great popularity of this test in clinical practice. However, the model of Marmarou et al. includes only intracranial compliance, CSF circulation, and vascular factors in the extracranial veins (i.e., venous sinus pressure), whereas the role of cerebral autoregulation and active CBV changes is not incorporated.

The use of more complex models, also covering some aspects of cerebrovascular regulation, may improve the interpretation of PVI tests. These models, however, cannot be solved by simple analytic formulas; hence, we must resort to an algorithmic approach. The latter is based on an iterative procedure for parameter estimation that minimizes a suitable cost function of the difference between model predictions and patient clinical data (5). This kind of approach was recently adopted by us for the interpretation of PVI tests in patients with acute brain damage (24). We suggested that not only intracranial compliance and CSF outflow resistance but also the gain and time constant of cerebral autoregulation can be estimated with sufficient accuracy starting from the ICP response to multiple PVI tests performed in rapid succession.

The model used in our previous work (24), however, is too complex and computationally onerous to be routinely used in a clinical setting. Hence, we recently developed a reduced model that incorporates the main relationships between ICP, CSF circulation, intracranial compliance, and arterial-arteriolar CBV changes in much simplified terms. With that model we were able to reproduce several important properties of ICP dynamics, such as the occurrence of plateau waves, the ICP increase after acute arterial hypotension, and the dependence of PVI on cerebral vessel response (25).

The aim of this study is to test whether the reduced model can be used for the analysis of real ICP tracings in patients with acute brain damage. In particular, we want to (1) check the capacity of the model to simulate...
and predict short-term ICP changes during PVI tests by adjusting only a few parameters (intracranial compliance, CSF outflow resistance, cerebral autoregulation gain, and time constant), 2) assess the accuracy of the parameter estimates obtained from real clinical data, and 3) inspect the possibility of discriminating between patients with normal and weak autoregulation by looking at the estimated parameter values and at their mutual correlation.

Finally, the main advantages and limitations of this approach are discussed, and lines for future investigation are pointed out.

METHODS

Clinical Procedure

ICP monitoring was instituted in comatose trauma patients admitted to an intensive care unit. The measurement was done through a system consisting of a ventricular catheter, a commercially available monitoring line (Cordis intraventricular pressure-monitoring catheter with stopcock, model 910–127), and a disposable transducer (monitoring kit MK5–04DTNVF, Abbott) connected to a Siemens monitor (Sirecust 1281 model 8791137). Arterial pressure was simultaneously measured through a catheter inserted into the radial artery with the same monitoring device adopted for the ICP measurement. Arterial CO2 pressure and arterial O2 content were carefully controlled in each patient; in particular, mild hyperventilation was used, keeping arterial PCO2 between 30–40 kPa, while arterial saturation of hemoglobin was kept at >97%. ICP and arterial pressure data were sent to a Macintosh IIcx computer through an analog-to-digital converter (MacLab, World Precision Instruments), sampled at a rate of 20 Hz, and stored in the hard disk. The sampling rate is acceptable, since the frequency content of pressure signals does not exceed 10 Hz. The silicone catheter was positioned in the surgical room; it was inserted into the frontal horn of a lateral ventricle and tunneled for ~5 cm under the scalp. All the pressure lines were filled with sterile saline; the transducer was zeroed, with the external acoustic meatus as a reference point. The pressure-volume maneuver consisted of the injection or withdrawal of 1–4 ml of saline, according to the bolus technique described by Marmarou et al. (18). In all the maneuvers the injection rate was ~0.66 ml/s. The patients were artificially ventilated and under continuous sedation; in the case of respiratory problems, myorelaxant drugs were added. The PVI was tested every 12 h for the duration of the ICP monitoring; to minimize the fluctuations of the waveform related to artificial ventilation, the injection or the withdrawal was done at the same point of the respiratory cycle, possibly during the expiration phase. During the testing and for 30 min before testing, every drug or nursing procedure that could influence the ICP was avoided. The clinical status of all patients examined in this study, including the Glasgow coma scale and computerized tomography scan, is shown in Table 1.

Model Identification

ICP tracings during PVI tests were analyzed in 20 patients with acute brain damage by means of the mathematical model presented previously (25). The analysis consisted of two parts: 1) identification of the main parameters through a best fit between the model and in vivo results and 2) analysis of the correlation between parameters to characterize the main mechanisms responsible for the observed ICP changes.

Table 1. Clinical status of patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Gender</th>
<th>Age, yr</th>
<th>GCS Admission</th>
<th>Best 1st day</th>
<th>CT Scan</th>
<th>ICP, mmHg</th>
<th>MAP, mmHg</th>
<th>CPP, mmHg</th>
<th>PVI</th>
<th>Modified GOS</th>
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<td>9</td>
<td>8</td>
<td>Contusions</td>
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<td>92</td>
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<td>58</td>
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<td>5</td>
<td>Contusions</td>
<td>24</td>
<td>50</td>
<td>109</td>
<td>84</td>
<td>50</td>
</tr>
<tr>
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<td>Contusions</td>
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<td>37</td>
<td>89</td>
<td>64</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>22</td>
<td>6</td>
<td>7</td>
<td>Subdural</td>
<td>24</td>
<td>59</td>
<td>101</td>
<td>66</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
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<td>5</td>
<td>5</td>
<td>Contusions</td>
<td>35</td>
<td>64</td>
<td>99</td>
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<td>8</td>
<td>Diffuse damage</td>
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<tr>
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<tr>
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<td>Diffuse damage</td>
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<tr>
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GCS admission, Glasgow coma scale evaluated at admission; GCS 1st day, best Glasgow coma scale score recorded during 1st day after trauma; CT scan diagnosis, diagnosis based on 1st computed tomographic scan performed at admission; Diffuse damage indicates signs of increased intracranial content (basal cisterns compressed or absent) with or without subarachnoid hemorrhage. ICP mean, mean intracranial pressure averaged over entire recording period; ICP max, maximum intracranial pressure, lasting >5 min, measured during entire recording period; MAP mean, mean arterial pressure averaged during entire recording period; MAP min, lowest arterial perfusion pressure, lasting >5 min, measured during entire recording period; CPP mean, mean cerebral perfusion pressure averaged during entire recording period; CPP min, lowest cerebral perfusion pressure, lasting >5 min, measured during entire recording period; PVI mean, mean pressure-volume index evaluated over all tests during recording period; PVI min, lowest pressure-volume index obtained over all tests performed during recording period; GOS, Glasgow outcome scale evaluated 6 mo after trauma through interview: GR/MD, good recovery or moderate disability; SD, severe disability; in 2 cases (patients 1 and 17) it was impossible to assess outcome.
Two preliminary elaborations were performed on each clinical tracing. First, because the model does not account for the pulsating changes in CBV induced by the sphygmic wave or by respiration, but it can only reproduce the low-frequency ICP pattern (25), the systemic arterial pressure (SAP) and ICP waveform have been numerically filtered. To eliminate the sphygmic wave, we used a low-pass finite impulse response (FIR) filter with 128 coefficients [designed with the Hamming window technique (16) and cutoff frequencies at 1 Hz], while the respiratory wave was eliminated by means of a 5-s moving-average filter. An example of the ICP and SAP tracings before and after filtration is shown in Fig. 1.

As clearly shown in Fig. 1, the ICP tracings exhibit some significant peaks, which are positive in correspondence with the bolus injection maneuvers and negative during bolus withdrawal. These peaks might be caused by force transmitted from the syringe into the cranial cavity or might represent the real instantaneous effect of the bolus on ICP; in the latter case, the bolus would cause a disproportionate instantaneous ICP change that, in a few seconds, is accommodated by volume redistribution along the neuraxis and/or by a decrease in cerebral venous blood volume. Because any other of these phenomena was included in the model, the portions of the ICP tracings containing peaks have been cut off (i.e., they have not been considered in the identification procedure).

Finally, the filtered ICP and SAP signals were stored in the computer at a sampling period of 1 Hz to be elaborated subsequently by means of the minimization algorithm. Sinus venous pressure was maintained constant (6 mmHg) throughout the simulations.

Parameter estimation. Model parameters were estimated through an automatic procedure. Starting from an initial guess, some model parameters suitably chosen a priori are iteratively modified by a numerical algorithm to minimize a cost function of the difference between the model and in vivo results. Because statistical information on the measurement errors was not available, we adopted the classic least-square cost function (5), i.e.

\[
F(\theta) = \sum_{i=1}^{N} [P_{ic}(t_i) - P_{ic}^{i}(\theta)]^2
\]

where \(P_{ic}(t_i)\) represents the filtered in vivo ICP value at the instant \(t_i\), \(P_{ic}^{i}(\theta)\) is ICP model prediction at the same instant, \(P_a\) and \(P_a^{i}(\theta)\) are the filtered SAP instant value and time derivative (to be used as inputs to the model), \(I_i\) is the bolus injection rate, \(N\) is the number of available data points, and \(\theta = [\theta_0, \theta_1, \ldots, \theta_k]^{T}\) is a vector of model parameters (including initial values of state variables) to be identified through the minimization algorithm.

The values of the parameters that warrant a local minimum for the cost function (i.e., \(\theta\)) are deemed to characterize the patient’s intracranial dynamics.

A crucial problem in the use of the minimization algorithm consists in the choice of the parameters to be optimized. Theoretically, all model parameters and all initial values of state variables should be adjusted in each patient to improve the fitting. The parameters of the model are the initial value of ICP and of arterial compliance \(P_{ic}(0)\) and \(C_a(0)\), respectively, the CSF formation and outflow resistances \(R_s\) and \(R_o\), the intracranial elastance coefficient \(k_e\), the central baseline and amplitude of the sphygmoid autoregulation characteristic and the autoregulation time constant \(G\), \(\Delta C_a\), \(\tau\), respectively), the basal value of compliance \(C_{sn}\), the basal CBF \(q_{sn}\), and the resistance of the large cerebral veins \(R_{pv}\).

However, when we are dealing with a parameter identification problem, the best compromise must be found among these different requirements: 1) a good fit between the model and experimental results (this generally improves by increasing the number of estimated parameters), 2) the accuracy of parameter estimates (this generally worsens with the number of parameters), and 3) the physiological and clinical relevance of the estimates.

To clarify these problems, we performed some preliminary computer tests by varying all the model parameters. These tests suggested that venous resistance plays a negligible role during PVI tests. Moreover, the same trials revealed that only \(R_{pv}/R_t\) can be identified with sufficient accuracy. For these reasons, \(R_{pv}\) and \(R_t\) were maintained at their basal level throughout the subsequent simulations. Furthermore, in most patients (with only 2 exceptions, see RESULTS) cerebral perfusion pressure (CPP) varied only by a few mmHg during PVI tests. Hence, just the central slope of the autoregulation characteristic, but not its saturation level, could be identified. For this reason, \(q_{sn}\) and \(\Delta C_a\) were maintained at their basal value throughout the simulations. Estimation of \(\Delta C_a\), however, was necessary to provide accurate reproduction of the ICP pattern in the two patients who exhibited ICP changes.

The parameters estimated in all patients were thus \(k_e\), \(R_{pv}\), \(G\), and \(\tau\). All these parameters summarize a different aspect of intracranial dynamics with distinct clinical implications. Finally, the parameter \(C_{sn}\), which represents the basal value of arterial-arteriolar compliance (hence, the basal value of CBV) was estimated in only one case. In most patients a good fit of the ICP tracings could be achieved by maintaining this parameter at its basal level.

Once a final least-square estimate was obtained using the iterative scheme, an approximate evaluation of the covariance matrix \(V(\hat{\theta})\) of the parameter estimates was computed by assuming (2, 5)

\[
V(\hat{\theta}) = \sigma^2[S^T S]^{-1}
\]

where \(\sigma^2\) denotes the variance of the measurement noise (assumed equal for all the data points) and \(S\) is the \(N \times p\) sensitivity matrix (where \(N\) is the number of data points and \(p\) is the number of parameters to be estimated) evaluated at
\[ \Theta = \hat{\Theta}, \text{i.e.} \]
\[
S = \left[ \frac{\partial P_{ic}(t, P_a(t), P_s(t), I_i, \Theta)}{\partial \Theta} \right]_{\Theta = \hat{\Theta}}
\]

The sensitivity matrix was computed using a forward difference approximation for the time derivatives (7). As usual, \( \sigma^2 \) was estimated through the following equation
\[
\sigma^2 = \frac{F(\hat{\Theta})}{N - p} = \frac{1}{N - p} \sum_{i=1}^{N} \left( P_{ic}(t) - P_{ic}(t, P_a(t), P_s(t), I_i, \hat{\Theta}) \right)^2
\]

Knowledge of the covariance matrix is of paramount importance in any identification problem, since it provides a method for evaluating the accuracy of parameter estimates. Basically, the ith diagonal element of the covariance matrix, \( v_i(\theta) \), represents the variance of the ith parameter estimate, \( \theta_i \). Starting from knowledge of the variance, the accuracy in the estimation of \( \theta_i \) was assessed by computing a 95% confidence interval for each estimated parameter, according to the following equation
\[
\hat{\theta_i} \pm \sqrt{v_i(\theta)} \cdot t_{0.975}(df)
\]

where df represents the degrees of freedom used in Student’s distribution, i.e., df = N − p.

All the numerical computations described above (parameter estimation, evaluation of the covariance matrix, evaluation of confidence intervals) were performed on 486 MS-DOS personal computers using the free software ADAPT II developed at the University of Southern California (7).

Analysis of the correlation between parameters. In many cases, inspecting the confidence intervals of the estimates represents only a partial analysis, which does not exploit all the information contained in the covariance matrix. As is well known, the nondiagonal elements of \( V \) [i.e., the elements \( v_{ij}(\theta) \), with \( i \neq j \)], which were not used in the previous equations, provide information on the mutual correlation between the parameters \( \theta_i \) and \( \theta_j \). As we attempt to demonstrate, analysis of this correlation may be of great clinical value in neurosurgical intensive care units.

A straightforward way for visualizing the correlation between parameters and for understanding its practical implications is to compute the so-called \( \epsilon \)-indifference regions of the parameter space. Let us assume that we have estimated the “best” values of model parameters (\( \theta \)); this is the value that minimizes the cost function \( F(\theta) \). A crucial question is, How much can we change the parameters simultaneously from their optimal value so that the cost function does not increase more than a given quantity \( \epsilon \)? In other words, we look for the region of the parameter space that satisfies the following disequation
\[
|F(\theta) - F(\hat{\Theta})| < \epsilon
\]  

The set of values of \( \theta \) that satisfies Eq. 2 are commonly referred to as the \( \epsilon \)-indifference region.

From our particular point of view, computation of the \( \epsilon \)-indifference region is meaningful, since it provides information on how the parameters of intracranial dynamics can be modified together without affecting the ICP time pattern significantly. Even more important, analysis of the \( \epsilon \)-indifference region permits us to make hypotheses on which concurrent changes in parameters may have the greatest effects on ICP, hence, may be particularly dangerous or particularly beneficial for the patient’s status.

The \( \epsilon \)-indifference region can be approximated, in a sufficiently small neighborhood of the optimal value \( \theta \) (i.e., if \( \epsilon \) is small enough), by the following disequation
\[
|d\Theta^T H d\Theta| < 2\epsilon
\]

where \( d\Theta \) denotes the vector of parameter changes with respect to the optimal value \( \Theta \), \( d\Theta = \Theta - \hat{\Theta} \) and \( H \) is the Hessian matrix evaluated at \( \Theta \). According to Bard (2), the Hessian matrix can be approximated by the reciprocal of the covariance matrix, i.e.
\[
H = \frac{1}{V(\hat{\Theta})^{-1}}
\]

Equation 3 represents a family of ellipsoids in the \( p \)-dimensional parameter space. The ellipsoids corresponding to different values of \( \epsilon \) are concentric, with equal shape and orientation; hence, the same essential information can be gained without paying attention to the particular value of \( \epsilon \). The ellipsoids can be visualized only when \( p \leq 3 \).

If only two parameters (i.e., \( \theta_i \) and \( \theta_j \) are allowed to change simultaneously while all the others are set at their optimal value, one can visualize a two-dimensional section of the \( \epsilon \)-indifference region. In the case of Eq. 3, this reduces to a simple ellipse.

In general, the orientation and the shape of these ellipses may be of importance (Fig. 2). If the axes of the ellipse are parallel to the \( \theta_i \) and \( \theta_j \) axes or if they have approximately the same length (Fig. 2B), the two parameters are uncorrelated. On the contrary, if the longest axis of the ellipse lies in the first and third quadrants of the plane (Fig. 2C), the two parameters are positively correlated; this means that the effect of increasing one parameter can be counterbalanced by decreasing the other. Finally, if the longest axis lies in the second and fourth quadrants (Fig. 2A), the two parameters are negatively correlated: in this case, the effect of increasing one parameter can be counterbalanced by decreasing the other. Moreover, the degree of correlation between parameters is significantly related to the eccentricity of the ellipse: the higher the eccentricity (i.e., the ratio of the longest to the shortest axis), the more closely correlated the two parameters are.

From a clinical point of view, it is of particular importance to examine the directions of the longest and shortest axes, especially when the ellipses have great eccentricity. If the two parameters are modified simultaneously (by a therapeutic maneuver or by a patient’s physiopathological change) so that their values move in the direction of the longest axis, the cost function exhibits only minor alterations; this means that the ICP time pattern is only scarcely sensitive to this particular combination of parameter changes. In contrast, if the two parameters vary simultaneously in the direction of the shortest axis, even small modifications in their values are able to elicit a considerable alteration in the cost function, hence, in the ICP time pattern.

Knowledge of the direction of maximum and minimum sensitivity for each parameter may be of clinical value to avoid improper maneuvers causing unpredictable ICP changes and to plan the optimal target therapy for the ICP control.

Finally, the different orientations and eccentricity of the \( \epsilon \)-indifference regions may enable better classification of patients and may provide suggestions on the main mechanisms responsible for ICP alterations during PVI tests (see RESULTS).
Only in a few instances can large values of confidence intervals be observed, indicating that the corresponding parameter is only poorly estimated with the ICP data available.

In Table 2, the $k_c$ values vary from about one-half of normal (which means good intracranial compliance) to more than twice normal (poor compliance). These values are in the range reported in the clinical literature for patients with various intracranial diseases (1, 8, 9).

$R_o$ is significantly increased in most patients. There is quite a strong correlation between basal ICP and $R_o$, suggesting that, in the model, CSF resistance is primarily responsible for sustained ICP. The $R_o$ values reported in Table 2 agree reasonably well with those measured by Gjerris et al. (11) and Kosteljanetz (15) but are significantly higher than those reported by Marmarou and co-workers (17). Nevertheless, in a few cases, the accuracy of parameter estimates is rather satisfactory. Only in a few instances can large values of confidence intervals be observed, indicating that the corresponding parameter is only poorly estimated with the ICP data available.

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In Table 2, the $k_c$ values vary from about one-half of normal (which means good intracranial compliance) to more than twice normal (poor compliance). These values are in the range reported in the clinical literature for patients with various intracranial diseases (1, 8, 9).

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patients (1, 5, and 7) $R_0$ could not be estimated (i.e., the algorithm did not converge or the confidence interval of this parameter was extremely high), because these patients did not exhibit a constant ICP baseline before the maneuver. The absence of a well-defined baseline does not permit identification of the model equilibrium level, which is mainly related to the status of CSF circulation. In these situations, the minimization algorithm was run by setting $R_0$ to a constant value that warrants an equilibrium level within the range of ICP fluctuations.

$G$ and $\tau$ show large differences among patients: whereas a few patients exhibit quite normal values of these parameters, others are characterized by a moderate or severe reduction in $G$ and/or by an increase in $\tau$. The large individual variability in the estimated autoregulation response suggested that we roughly classify patients into three different classes: those with effective and prompt autoregulation ($G/G_0 > 0.2$, $\tau/\tau_0 < 2$), those with effective but slow autoregulation ($G/G_0 > 0.2$, $\tau/\tau_0 > 2$), and those with weak autoregulation ($G/G_0 < 0.2$). This classification, of course, is just indicative. As discussed in $\varepsilon$-Indifference Regions, better classification can be achieved by including the arterial-arteriolar blood volume among the estimated parameters and looking at the mutual correlation between the estimates.

Three examples of ICP tracings in patients classified with weak autoregulation are shown in Fig. 3. In these cases the ICP response to the maneuver shows a monotonic return toward the initial level (i.e., a monotonic decrease after bolus injection and a monotonic increase after bolus withdrawal), as in the classic model of Marmarou et al. (18, 19). In patient 4 the ICP response is also significantly modulated by the simultaneous decrease in SAP. The latter causes a passive reduction in CBV, which speeds the ICP decrease after bolus injection and opposes the ICP return to baseline after bolus withdrawal.

A few examples of ICP tracings in patients with preserved autoregulation are shown in Fig. 4, where patients 8 and 14 are characterized by efficient and prompt autoregulation: after the bolus injection, ICP exhibits a sudden paradoxical response, which does, however, last for only a few seconds. After this period, active CBV changes are completed, and so the ICP progressively returns to the initial level owing to a prevalence of the CSF compensatory mechanisms. In contrast, patient 3 is classified as having efficient but slow autoregulation: the paradoxical response develops progressively during the first minutes after the maneuver, according to the high $\tau$. Finally, patient 10 exhibits intermediate characteristics.

In 2 of 20 patients (i.e., patients 5 and 9) CPP (CPP = SAP − ICP) displayed a significant reduction during PVI tests, approaching the autoregulation lower limit (50–60 mmHg). In these cases, reproduction of the ICP time patterns required identification not only of $G$ but also of its saturation level. Moreover, in the case of patient 9, we also identified the total arteriolar blood volume. The results for these two patients are shown in Figs. 5 and 6 and are separately discussed below, since they are representative of the behavior of ICP at low CPP values close to the stability boundary.
Figure 5 shows that the ICP of patient 9 exhibits only a modest increase after the first bolus injection maneuver and a disproportionate increase after the second injection. The model ascribes the latter increase to the spontaneous SAP reduction during the final portion of the PVI test. As a consequence of the decrease in SAP, CPP approaches the lower autoregulation limit (84 ± 25 mmHg). In this pressure range, even a small fall in CPP is able to evoke a large increase in CBV (see Fig. 4 in Ref. 25), which, in turn, may be responsible for the disproportionate rise in ICP.

The ICP time pattern in patient 5 (Fig. 6) is similar to that of a single aborted plateau wave. In this patient the bolus injection evokes an abrupt vasodilation and a consequent dramatic rise in ICP to ~50 mmHg. As a consequence, CPP falls below the autoregulation lower limit (CPP = 94 - 50 = 44 mmHg), a value that is maintained reasonably constant for >1 min. Finally, the bolus withdrawal causes a sudden vasoconstriction and the immediate restoration of ICP to a level quite close to the initial one. The slow increase in ICP evident in the last portion of the clinical tracing can be ascribed to a gradual vasodilation induced by the concomitant lowering of SAP.

**e-Indifference Regions**

As discussed in METHODS, analysis of the mutual correlation between the parameter estimates and the construction of e-indifference regions may be useful in reaching a more rigorous classification of patients and in formulating hypotheses on combinations of parameters that may have greater impact on ICP.

When investigating the mutual correlation between the parameters, however, we found that it was very beneficial to estimate not only $R_o$, $k_E$, the autoregulation central slope, and $\tau$ (which are the 4 parameters shown in Table 2), but also the total arterial-arteriolar blood volume (i.e., the basal value of arterial-arteriolar compliance). Inclusion of this additional parameter only scarcely improves the quality of fitting and worsens the accuracy of parameter estimates, but analysis of its correlation with the other parameters is worthwhile to discriminate between patients with strong and those with weak autoregulation.

For example, Fig. 7 shows some of the two-dimensional 5% indifference regions (obtained through Eq. 3) in patients 4 and 11 (weak autoregulation). The same indifference regions are shown in Fig. 8 for patients 3 and 9 (strong autoregulation). As clearly shown in Figs. 7 and 8, the orientation of most ellipses (hence, the correlation between parameters) is different in patients with weak and strong autoregulation. The reasons for these differences are briefly analyzed below.

For simplicity, we focus attention only on the ICP time pattern after a bolus injection maneuver. Similar analyses can also be developed, of course, with reference to bolus withdrawal.

Correlation between the $k_E$ and $R_o$. These two parameters exhibit a positive correlation in patients with weak autoregulation. In these patients, in fact, the return of ICP toward the baseline after bolus injection occurs according to a simple compliance plus resistance model; as is well known, the time constant of such a model is proportional to $R_o/k_E$. Hence, an identical time
constant can be obtained by increasing $R_o$ and $k_E$ concurrently. In contrast, in patients with preserved autoregulation, an increase in $k_E$ causes amplification of the paradoxical response to bolus injection, i.e., a further delayed ICP increase. The latter can be counteracted by improving CSF outflow, i.e., by decreasing $R_o$. The two parameters are thus inversely correlated in these patients.

Correlation between $G$ and $R_o$. In Figs. 7 and 8, one can observe a negative correlation between these two parameters in the weak and strong autoregulation cases. In patients with weak autoregulation, an increase in $G$ is reflected in an increase in CBF, which, in turn, causes an increased capillary pressure and an increased CSF production rate. The latter can be compensated for by decreasing $R_o$. In patients with preserved autoregulation, increasing $G$ causes, besides the previous phenomenon, a stronger paradoxical increase in ICP after bolus injection. Both phenomena can be reduced by raising the CSF outflow, i.e., decreasing $R_o$.

Correlation between $G$ and $k_E$. In patients with preserved autoregulation, these two parameters are inversely correlated. Increasing $G$ causes a vasodilation after bolus injection, with a consequent paradoxical increase in ICP. The latter can be compensated for by increasing the intracranial compliance, i.e., reducing $k_E$. In contrast, a clear correlation cannot be found in patients with weak autoregulation, where low eccentricity and contradictory orientation of the ellipses are observed.

Correlation of $C_{an}$ with $k_E$, $R_o$, and $G$. As clearly shown in Fig. 7, in patients with weak autoregulation the correlation between $C_{an}$ and the other three parameters is generally positive. Increasing $C_{an}$ in the model means working with higher values of arterial-arteriolar blood volume. After a bolus injection, blood volume decreases passively in these patients, thus buffering the rise in ICP. The opposite effect (i.e., a further rise in ICP) occurs if $R_o$ and/or $G$ is increased. In these patients, however, the correlation between $C_{an}$ and $k_E$ is scanty. In contrast, in patients with strong autoregulation a higher arterial-arteriolar blood volume (hence, a higher $C_{an}$) causes a stronger paradoxical response after bolus injection. The latter can be attenuated by reducing $R_o$, i.e., permitting a more rapid CSF outflow.
by reducing $k_E$, i.e., increasing intracranial compliance, or by reducing $G$. Hence, in these patients, $C_{an}$ is inversely correlated with the other three parameters, as demonstrated by the inclination of the ellipses in Fig. 8.

**DISCUSSION**

The main result of the present work is that the proposed simple mathematical model of intracranial dynamics can reproduce the time pattern of ICP during PVI tests reasonably well by adjustment of only a few parameters with a clear clinical and physiological significance. Moreover, the model suggests that ICP during PVI tests contains information useful in characterizing not only CSF dynamics and intracranial elastance but also the status of cerebrovascular autoregulation. Analysis of clinical tracings may permit hypotheses to be formulated on the most influential short-term mechanisms affecting ICP in a given patient and to point out their mutual relationships.

Traditionally, PVI tests are explained in terms of an intracranial compliance, loaded by a volume bolus, that progressively empties through the CSF circulatory pathways. This model gives rise to a simple monoexponential analytic relationship linking ICP during PVI tests to $k_E$ and to $R_o$ (18, 19). The clinical data available, however, suggest that the previous concepts are often oversimplified and can fail to grasp some important
aspects of the ICP response, especially in patients with strong autoregulation mechanisms. Only in a limited number of cases does ICP exhibit a monotonic trend after the bolus injection or withdrawal maneuver, similar to that hypothesized in the traditional models. Consequently, we claim that more complex models are needed for the interpretation of PVI tests, also including some aspects of cerebral hemodynamics and CBV autoregulation adjustments.

During PVI tests, active CBV variations often manifest themselves through a paradoxical response, i.e., a delayed ICP increase after bolus injection and a delayed ICP reduction after withdrawal, through a mechanism analogous to the vasodilatory cascade described by Rosner and Becker (22). Although, in general, a monotonic trend is characteristic of weak autoregulation whereas paradoxical responses are typical of patients with strong autoregulation, one must be aware that the ICP time pattern can also be significantly modulated by arterial pressure alterations during the trial (Figs. 3, 5, and 6). A correct classification of patients cannot be achieved simply by looking at the morphology of the ICP response, but by providing an overall fit of the model to clinical data and looking at the numerical values and mutual correlation of parameter estimates.

In 18 of 20 patients some portions of the ICP tracings were analyzed in a previous work by using a more complex model of the ICP dynamics (24). The results obtained here substantially confirm those reported

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Fig. 8. 5% Indifference regions showing correlation between 2 parameters and effect of their simultaneous change on ICP in 2 patients with strong autoregulation (patients 3 (A) and 9 (B)). x- and y-Axes, parameter percent changes with respect to optimal value computed with minimization algorithm. Inside region, cost function varies by <5% i.e., ICP changes are quite negligible. There is a negative correlation between all examined parameters, because in preserved autoregulation case, increasing any of these parameters causes ICP to change in same direction.
previously concerning the good fit and the kind of patient classification achieved. The significant improvement of the present study relative to the earlier study consists in far less computational effort being required to achieve parameter estimates owing to the drastic reduction in model complexity. We demonstrated that a reliable interpretation of PVI tests can be obtained by incorporating only a few fundamental mechanisms: a nonlinear storage capacity, CSF outflow, and an arterial-arteriolar compliance actively regulated by CBF changes. The possibility of using a reduced model without evident deterioration in its performance is of primary importance if one intends to apply the parameter estimation procedure directly in a clinical setting. Indeed, the complete model utilized previously (24) was too complex and computationally heavy to be of direct clinical advantage.

The parameter values estimated in this work agree quite closely with those reported in the clinical and physiological literature. The $k_i$ is $0.05–0.25$ ml·m⁻¹ (Table 1). According to various authors (1, 8, 9), normal values for $k_i$ are $0.05–0.15$ ml·m⁻¹, whereas values as high as $0.25$ ml·m⁻¹ are often found in patients with severe brain disorders.

$R_o$ is elevated in most patients (except patient 13, who exhibits a normal CSF outflow). In general, one can find quite a close relationship in our model between the basal ICP and $R_o$. This result agrees with the observations by Gjerris et al. (10, 11), Kosteljanetz (15), and Hansen et al. (14), who found a close correspondence between the measured ICP and $R_o$ in patients with hydrocephalus and acute subarachnoid hemorrhage. In the present work most values of $R_o$ are in the range $9.3–94.3$ mmHg·ml⁻¹·min, except for patients 5 and 20, who have values as high as $132$ and $175$ mmHg·ml⁻¹·min, respectively. Similar values of $R_o$ were reported by Hansen et al. (52–100 mmHg·ml⁻¹·min), Kosteljanetz (11.5–85 mmHg·ml⁻¹·min), and Borgeisen et al. (3) (6.66–111.11 mmHg·ml⁻¹·min). In contrast, our results are in agreement with the observations by Marmarou et al. (17), who found lower values of $R_o$ (2.25–28.58 mmHg·ml⁻¹·min) in head-injured patients. Their values were able to account for only about one-third of the rise in ICP. The previous discrepancies might partly be imputable to differences between the steady-state infusions in the model and/or in the identification procedure.

According to the previous analysis, in the present work the main mechanism responsible for sustained ICP elevation is the increase in $R_o$. Furthermore, the mean ICP level in the model is also affected by CBF, hence, by the status of autoregulation mechanisms. CBF influences the CSF production rate through a change in intravascular pressure at the capillary level. Of course, there may be other mechanisms that elevate ICP and that have not been tested in this work, and they may become the subject of future refinements in the model and in the identification procedure. For instance, an increase in central venous pressure may affect ICP via a reduction in CSF outflow without the need for an increased resistance. This factor has not been included in this study, since, because of the lack of data, venous sinus pressure was maintained constant throughout the identification trials. Furthermore, changes in the osmotic pressure gradient may modulate CSF exchange at the capillary wall and may have sustained effects on ICP. Sustained ICP elevations in closed-head injury may also be the result of various mechanisms leading to increased intracranial content. These are often not well identified in clinical practice and are usually combined. Surgical masses, such as intracranial hematomas, are present in a relevant percentage of cases, and their expansion accounts for acute increases of ICP. In cases with focal lesions, such as cerebral contusions, the accumulation of fluid in the area surrounding the damaged tissue, mainly due to blood-brain barrier opening, may cause a significant rise in ICP. In diffuse damage it is more likely that a combination of vascular and nonvascular mechanisms causes an increase in intracranial content. Surgical masses have been identified and promptly evacuated in our cases; all our studies have been performed in a stable clinical situation, in which it may be assumed that a steady state has been reached.

In 12 of 20 patients the model ascribes part of the ICP response to active CBV changes induced by autoregulation mechanisms. In fact, these patients have quite a high autoregulation gain. In contrast, eight patients are classified as having weak autoregulation, since their autoregulation gain is lower than one-fifth of the basal value [the basal value of the autoregulation gain was assigned previously (25) as that value that warrants a constant CBF within the autoregulation range]. Finally, two patients classified with efficient autoregulation exhibit a significant increase in $\tau$ ($\tau \approx 40$ s in patient 3 and $\tau$ of a few minutes in patient 2). More generally, $\tau$ displays a large variability in the patients of the autoregulated group, ranging from a few seconds...
to several 10ths of a second. The previous data confirm that autoregulation may be significantly altered in acute brain damage, a result reported by several authors (6, 21). Differences between prompt and delayed autoregulation might be ascribed to damage of neural control pathways (which generally have time constants of a few seconds), which are possibly replaced by the action of slower metabolic or chemical feedback mechanisms (20).

An important new element of the present work consists in the analysis of $\epsilon$-indifference regions and of the corresponding correlation between parameter estimates. Although this technique is frequently used in engineering textbooks concurrently with identification problems (2), it has been applied only rarely in clinical practice until now. In our opinion, two main benefits encourage the use of this technique when the ICP patterns of patients with severe brain damage are analyzed.

1) By looking at the shape and orientation of the ellipses, one can formulate hypotheses on deep pathophysiological mechanisms responsible for ICP changes and, on this basis, attempt better patient classification. In Figs. 7 and 8 we demonstrated that patients can be differentiated by observing the orientation of the ellipses linking $k_e$ with $R_o$, $C_{an}$ with $R_o$, and $C_{an}$ with $G$. A positive orientation is indicative of a prevalence of passive blood volume changes, hence, of weak autoregulation; a negative orientation suggests the prevalence of active blood volume alterations, hence, strong autoregulation mechanisms. The use of this criterion to differentiate patients in two classes leads to the same classification that can be achieved by looking at the autoregulation gain in Table 2, if $G/G_0 = 0.2$ is used for the classification threshold (i.e., if one assumes that patients with weak autoregulation have a gain smaller than $\frac{1}{5}$ of normal). Hence, the choice of this previous value for the classification threshold can be justified a posteriori as the value that warrants the best agreement between the classification and ellipse orientation.

2) Examination of the longer and shorter axes of the ellipses may permit the directions of maximum ICP sensitivity to parameter changes to be discerned. In perspective, this information might be exploited to design improved therapies for intracranial hypertension and to avoid inappropriate maneuvers in patients that risk acute ICP increase.

The previous possibilities arise from the definition of the $\epsilon$-indifference region, i.e., the region of the parameter space where the cost function, $F(\theta)$, exhibits only minor changes (below the threshold, $\epsilon$) with respect to its optimum value. Because, according to Eq. 1, the cost function in our study depends only on the difference between model and clinical ICP, the $\epsilon$-indifference region can be regarded as a region of relative insensitivity of ICP to parameter alterations. Moving along the longer axis, it is possible to modify parameters in a wide range without causing large alterations in ICP. In contrast, even a small parameter change in the direction of the shorter axis may have serious effects on ICP. The differences between the axis directions become more evident the more eccentric the ellipses are. Of course, the shorter axis gives only a clue of the direction of maximum ICP sensitivity. Whether ICP is actually increasing or decreasing depends on the movement along the axis.

The ellipses in Fig. 7 demonstrate that, in patients with weak autoregulation, the most important mechanism capable of buffering ICP changes is the passive blood volume alteration. Even a small decrease in $C_{an}$, which reduces the arterial blood volume initially contained in the craniospinal space, or a small increase in $G$, which makes the cerebrovascular bed behave less passively, may cause an important rise in the ICP response. This result agrees with findings of Gray and Rosner (12, 13), who observed a dramatic increase in PVI, hence, an improvement in the ICP response to bolus injection, when moving outside the autoregulation range. In contrast, in patients with strong autoregulation, active blood volume changes may induce paradoxical responses; as suggested by the direction of the shorter axes in Fig. 8, the paradoxical responses may be sharply amplified by an increase in the arterial-arteriolar basal compliance, $G$, $k_e$, and $R_o$. In the most serious cases (i.e., patient 5 in Fig. 6) paradoxical responses may cause uncontrolled ICP increases similar to those occurring during the development of plateau waves. The previous considerations emphasize that patients with excessive cerebrovascular reactivity, reduced intracranial compliance, and poor CSF circulation may risk intracranial hypertension, and so any manipulation on these patients should be performed with extreme caution in intensive care units. Preliminary statistical tests performed on a wider patient population (34 patients) confirmed this result, indicating that patients with paradoxical responses to PVI tests generally have a worse outcome (23).

Finally, it is to be stressed that the previous analysis concerns only the acute ICP response to a bolus volume load; hence, it is indicative of only short-term intracranial dynamics. The model’s usefulness lies in the possibility to reach a quantitative estimate of parameter values and to assess the tendency of the patient to develop uncontrolled acute intracranial hypertension in response to sudden perturbations. The possible role of other long-term mechanisms affecting ICP (e.g., osmosis, brain edema, tissue metabolism) has not been considered in the model, and so model simulation results cannot be used to achieve long-term forecasting of ICP derangement.

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