Krzysztof Cieslicki

Mathematical Modelling of the Infusion Test

Institute of Automatic Control and Robotics, Warsaw University of Technology,
A. Boboli 8, 02-525 Warsaw, Poland
e-mail: k.cieslicki@mchtr.pw.edu.pl

The objective of this paper was to improve the well established in clinical practice Marmarou model for intracranial volume-pressure compensation by adding the pulsatile components. It was demonstrated that complicated pulsation and growth in intracranial pressure during infusion test could be successfully modeled by the relatively simple analytical expression derived in this paper. The CSF dynamics were tested in 25 patients with clinical symptoms of hydrocephalus. Basing on the frequency spectrum of the patient's baseline pressure and identified parameters of CSF dynamic, for each patient an "ideal" infusion test curve free from artefacts and slow waves was simulated. The degree of correlation between simulated and real curves obtained from clinical observations gave insight into the adequacy of assumptions of Marmarou model. The proposed method of infusion tests analysis designates more exactly the value of the reference pressure, which is usually treated as a secondary and of uncertain significance. The properly identified value of the reference pressure decides on the degree of pulsation amplitude growth during IT, as well as on the value of elastance coefficient. The artificially generated tests with various pulsation components were also applied to examine the correctness of the used algorithm of identification of the original Marmarou model parameters.

Key words: infusion test, pulsatile and respiratory waves, mathematical modeling, hydrocephalus.

Introduction

The requirement for an infusion test (IT) often arises with suspicion of communicating hydrocephalus, in which the imaging is unable to confirm obstacles in the cerebrospinal liquid flow between the ventricular system and the subarachnoid space. In spite of its

invasiveness (access to the liquid spaces is most often executed with the help of lumbar puncture), IT still remains one of the most important diagnostic tools in this illness [5]. In clinical practice, the most frequently applied test is constant-rate infusion of the normal saline into the subarachnoid space. A mathematical description of the rise of ICP during IT was first proposed by Marmarou [17] with further small modifications introduced by Avezaat [3]. This work has subsequently formed the basis of well-established clinical diagnostic investigations.

Although Marmarou model expresses a rational compromise between the huge complexity of physiological and pathophysiological processes and the limited possibility for their quantitative description, it does not take into account the pulsatile and respiratory waves, which are always present in the IT signals. Periodic changes of the cerebral arterial blood volume and changes of venous outflow generated by respiration are transmitted into fluctuations of ICP around the mean value due to the stiffness of the skull. By the early 1950s, it was found that arterial pulse pressures are mainly responsible for the shape of the ICP wave [6]. With each contraction of the heart, a pressure wave is generated which travels along the arteries and provokes an intracranial pressure rise due to an enlargement of the arterial bed. In the frequency domain, the pulse waveform has several harmonic components; the fundamental component having a frequency equal to the heart rate. In turn, respiratory oscillations can be related to disturbances in the venous outflow from the brain. The venous system from the superior vena cava to the cerebral veins is valveless, except the ostium of the internal jugular vein to the brachiocephalic vein. During mechanical respiration, the inflow of air to the lungs provokes an increase in the intrathoracic pressure with simultaneous compression of large veins. This slows the flow of blood from the head and neck to the thorax, simultaneously increasing the pressure in the internal jugular veins which are a continuation of the sigmoid sinuses. The sigmoid sinuses are, in turn, a continuation of the transverse sinuses - branches of the superior sagittal sinus (SSS). Due to slowing of the blood flow through the sinuses, the outflow from the brain is limited and causes an increase of blood volume which remains in the veins, because the arterial inflow is continuous. During expiration, the reverse mechanism may be observed: the intrathoracic pressure diminishes, the veins enlarge, and the outflow of blood from the brain grows. The same situation is observed with physiological respiration but in reverse order. During inspiration, the volume of the veins decrease while during expiration it increases. These oscillations are related to the pressure oscillation in the SSS.

The formulation of mathematical models to explain the dependence between the circulation of the blood and the cerebrospinal fluid has interested many researchers. Various models of differing degrees of complexity have been proposed in the literature. These range from the simplest linear models [1, 13, 22, 23, 26] that can only reproduce limited phenomena, to complex non-linear models which can capture clinical observations more accurately [27, 28, 10, 11, 14, 21]. Linear models are often limited to the analysis of very small changes in the described quantities. Conversely, non-linear models, based on the solution of simultaneous differential equations [16], are often difficult to analyze and interpret. A mathematical theory called *systems analysis* has also been used to describe the relationship between arterial blood pressure (ABP) and ICP waveform. In this approach, the intracranial compartment can be considered to be a black box, which is described by its transformation of the input signal (ABP) into the output signal (ICP) [24]. The signals can be identified in the frequency [7] or time-domains [18] or in both domains [4].

The main goal of the present work is to incorporate the vascular and respiratory components into the generally-accepted Marmarou model of intracranial volume-pressure compensation. The study offers the possibility of developing, for each individual case an “ideal” infusion test curve free from artefacts and slow waves of various origin and compares it with a real curve from clinical observations. The degree of correlation of both curves gives some insight not only into the adequacy of assumptions of Marmarou model in the considered case but also on checking correctness of identified parameters of cerebrospinal fluid hydrodynamics.

Mathematical model

Model formulation

Recalling the well-known procedure of the Marmarou model evaluation, we may assume that from continuity requirements and within the time horizon of IT (of order of 15-30 min), the production of cerebrospinal fluid (CSF), Q_P , and the external infusion, Q_i , is balanced by reabsorption, Q_R , and storage, Q_S so that:

$$Q_P + Q_i = Q_R + Q_S \quad (1)$$

The intensity of reabsorption of CSF is given by the formula presented by Davson [17]:

$$Q_R = \frac{p - p_{SS}}{R} \quad (2)$$

in which p_{SS} [mmHg] denotes the saggital sinus pressure and R [mmHg/ml/min], is the resistance of CSF reabsorption.

In turn, the storage of CSF may be calculated from the relation

$$Q_S(t) = C(p) \cdot \frac{dp}{dt} \quad (3)$$

In the above expressions, $C(p)$ [ml/mmHg] is the pressure dependent intracranial compliance. Above a certain ICP level, the cerebrospinal space compliance decreases with ICP growth according to the relation:

$$C(p) = \frac{1}{E(p - p_0)} \quad (4)$$

where E [1/ml] describes the cerebral elasticity and p_0 [mmHg] is the so-called reference pressure.

Due to the heart action, arterial pressure, $p_A(t)$, pulsate around the mean value, p_{A0} . The simplest model of such pulsation, may be written in the form of a sinusoidal perturbation of amplitude δp_A superimposed on the mean value of arterial pressure:

$$p_A(t) = p_{A0} + \delta p_A \cdot \sin(\omega_1 t) \quad (5)$$

where ω_1 denotes the heart rate angular frequency.

Assuming that the compliance of cerebral arterial walls equals C_A , we may now estimate cerebral blood volume changes, δQ_A from the dependence:

$$\delta Q_A(t) \approx C_A \cdot \frac{d(p_A - p_{SS0})}{dt} = \omega_1 C_A \delta p_A \cos(\omega_1 t) \quad (6)$$

where p_{SS0} is the mean value of the saggital sinus pressure.

Within the very short time horizon (of order of a single heart beat period) it is reasonable to assume, that periodical fluctuations of arterial cerebral blood volume, δQ_A [ml/s], are balanced by periodical fluctuations of CSF volume, δQ [ml/s], (i.e. $\delta Q \approx \delta Q_A$). Consequently, we shall treat CSF secretion, $Q_P(t)$, as the pulsating function of time and write it simply in the form:

$$Q_P(t) = Q_{P0} + \omega_1 C_A \delta p_A \cdot \cos(\omega_1 t) \quad (7)$$

in which Q_{P0} denotes the rate of CSF production.

Simultaneously, we assume that due to respiration, the sagittal sinus pressure oscillates around the mean value, p_{SS0} , according to the formulae:

$$p_{SS}(t) = p_{SS0} + \delta p_R \cdot \cos(\omega_2 t) \quad (8)$$

where:

ω_2 denotes the angular frequency of respiration and

δp_R is the amplitude of pulsation of the sagittal sinus pressure.

Inserting equations (2), (3), (7) into (1) and bearing in mind (4) and (8) we obtain, after rearrangement, the subsequent differential equation describing ICP dynamic during the constant rate infusion:

$$\frac{dp}{dt} = -\frac{E}{R}(p - p_0)[p - p'_{B0} - RC_A \delta p_R \cos(\omega_1 t) - \delta p_R \cos(\omega_2 t)] \quad (9)$$

where:

$$p'_{B0} = p_{SS0} + R(Q_{P0} + Q_i) = p_{B0} + R \cdot Q_i \quad (10)$$

$$p_{B0} = p_{SS0} + R \cdot Q_{P0} \quad (11)$$

Equations (10) and (11) define the average values of two steady states of ICP, namely: the final plateau pressure, p'_{B0} , and the baseline pressure, p_{B0} , respectively.

In the category of differential equations, relationship (9) expresses the general case of Bernoulli's equation [19]. However, its right-hand side depends not only on the intracranial pressure, p , but also on time, t , in contrast to Marmarou's model. The model

Figure 1. Electrical model of CSF circulation with arterial and respiratory waves.

described by equation (9) may be presented in the form of its electric equivalent, shown in Figure 1, to help understanding.

Introducing the new variable P

$$P = p - p_0 \quad (12)$$

equation (9) takes the shape:

$$\frac{dp}{dt} = f(t) \cdot P + g(t) \cdot P^2 \quad (13)$$

in which

$$f(t) = \frac{E}{R} [p'_{B0} - p_0 + RC_A \omega_1 \delta p_A \cos(\omega_1 t) + \delta p_R \cos(\omega_2 t)] \quad (14)$$

$$g(t) = -\frac{E}{R} = \text{const} \quad (15)$$

It is possible to seek the general solution of equation (13), for any functions $f(t)$, $g(t)$, in the form [19]:

$$P(t) = \frac{1}{Y_1(t) + Y_2(t)} \quad (16)$$

where:

$$Y_1(t) = B \cdot e^{\Phi(t)} \quad (17)$$

$$Y_2(t) = -\Phi(t) \int g(t) e^{-\Phi(t)} dt \quad (18)$$

$$\Phi(t) = -\int f(t) dt \quad (19)$$

B – integration constant.

Putting (14) into (19) and performing integration we obtain:

$$\Phi(t) = -[\alpha t + \gamma_1 \sin(\omega_1 t) + \gamma_2 \sin(\omega_2 t)] \quad (20)$$

in which

$$\alpha = \frac{E}{R}(p'_{B0} - p_0) = \frac{EQ_i(p'_{B0} - p_0)}{(p'_{B0} - p_{B0})}, \gamma_1 = EC_A \delta p_A, \gamma_2 = \frac{Ep_R}{R\omega_2}. \quad (21)$$

When

$$\gamma_1 \ll 1 \text{ and } \gamma_2 \ll 1 \quad (22)$$

the following approximation is correct:

$$e^{-\gamma \sin(\omega t)} \approx 1 - \gamma \sin(\omega t) \quad (23)$$

Applying it to find the integral appearing in the rhs of (18), after lengthy calculation we obtain the approximate solution of equation (13) in the form:

$$P(t) \approx \frac{e^{[\gamma_1 \sin(\omega_1 t) + \gamma_2 \sin(\omega_2 t)]}}{Be^{-\alpha t} + D + G \sin(\omega_1 t - \beta) + H \sin(\omega_2 t - \xi) + K \cos(\Omega_1 t - \vartheta) + M \cos(\Omega_2 t - \chi)} \quad (24)$$

in which:

$$D = \frac{1}{p'_B - p_0}, G = \frac{\gamma_1}{\sqrt{\alpha^2 + \omega_1^2}}, H = \frac{\gamma_2}{\sqrt{\alpha^2 + \omega_2^2}}, K = \frac{\gamma_1 \gamma_2}{\sqrt{\alpha^2 + \Omega_1^2}}, M = \frac{\gamma_1 \gamma_2}{\sqrt{\alpha^2 + \Omega_2^2}},$$

$$\beta = \arctg \frac{\omega_1}{\alpha}, \xi = \arctg \frac{\omega_2}{\alpha}, \vartheta = \arctg \frac{\Omega_1}{\alpha}, \chi = \arctg \frac{\Omega_2}{\alpha}, \Omega_1 = \omega_1 - \omega_2, \Omega_2 = \omega_1 + \omega_2. \quad (25)$$

In view of inequalities (22) and because

$$\omega_1 \gg 1, \omega_2 \gg 1, \Omega_1 \gg 1, \Omega_2 \gg 1, \quad (26)$$

the following estimations are satisfied:

$$G \ll 1, H \ll 1, K \ll 1, M \ll 1. \quad (27)$$

Therefore, the solution, (24), may be further simplified to the following form:

$$P(t) \approx \frac{e^{[\gamma_1 \sin(\omega_1 t) + \gamma_2 \sin(\omega_2 t)]}}{Be^{-\alpha t} + \frac{1}{p'_{B0} - p_0}} \quad (28)$$

Bearing in mind the initial condition:

$$P(0) = p_{B0} - p_0 \quad (29)$$

We obtain the approximate analytical solution of equation (9) in the final form:

$$p(t) \approx p_0 + \frac{(p_{B0} - p_0)(p'_{B0} - p_0) \cdot [\exp \gamma_1 \sin(\omega_1 t) + \gamma_2 \sin(\omega_2 t)]}{(p_{B0} - p_0) + (p'_{B0} - p_{B0}) \exp \left[-\frac{EQ_i(p'_{B0} - p_0)}{(p'_{B0} - p_{B0})} t \right]} \quad (30)$$

which is valid provided both coefficients of pulsation, γ_1 and γ_2 , are much less than unity (of order of 0.1). To the authors' best knowledge, the solution has not been previously presented.

Model behavior

In spite of the nonlinearity and complexity of equation (9), its approximate analytical solution (30), is relatively simple. It is also worth noting, that in a similar manner to linear systems, both additive sinusoidal perturbation components also appear in the solution in additive form. This occurs because the other oscillating terms present in the solution (24) can be neglected. The additive property of the perturbation is a very important feature of the present model, since it is easy to substitute the simple sinusoidal perturbations of Q_{p0} and p_{SS0} by more complex periodic functions that are closer to reality.

From equation (30) and taking into consideration expressions (4), and (21), it can be shown that before an infusion test begins, ($Q_i = 0$) the ICP oscillates around the baseline value, p_{B0} , according to the following formula:

$$\begin{aligned} p_B(t) &= p_{B0} + (p_{B0} - p_0) [\exp \gamma_1 \sin(\omega_1 t) + \gamma_2 \sin(\omega_2 t) - 1] \cong \\ &\cong p + \frac{C_A}{C(p_{B0})} \delta p_A \sin(\omega_1 t) + \frac{1}{\omega_2 RC(p_{B0})} \delta p_R \sin(\omega_2 t) \end{aligned} \quad (31)$$

From the above formula it is clear that the vascular component of ICP remains in phase with arterial pressure oscillations. In contrast, the respiratory component of ICP lags the sagittal sinus pressure, p_{SS} , by the phase angle of 90° . In addition, the amplitude of the ICP pulse increases linearly with ICP and when it reaches the final plateau, both components of pulsation will be $(p'_{B0} - p_0)/(p_{B0} - p_0)$ times higher, than their initial amplitudes.

In the simplest case, of no pulsatile and respiratory waves both coefficients of pulsation γ_1 and γ_2 equal zero and equation (30) takes the well known form obtained by Marmarou [17]:

$$p_M(t) = p_0 + \frac{(p_{B0} - p_0)(p'_{B0} - p_0)}{(p_{B0} - p_0) + (p'_{B0} - p_{B0}) \exp \left[-\frac{EQ_i(p'_{B0} - p_0)}{(p'_{B0} - p_{B0})} t \right]} \quad (32)$$

Figure 2 matches the theoretical ICP growth calculated from Marmarou's model, (32), for two typical infusion rates: $Q_i = 1$ ml/min and $Q_i = 2$ ml/min (continuous lines), to those obtained from equation (30) with pulsation coefficients equal to

Figure 2. Comparison of theoretical ICP growth during IT calculated from the derived equation (34) with Marmarou's model (32) (continuous line).

$\gamma_1 = 0.05$ and $\gamma_2 = 0.01$. It can be seen that the amplitude of pulsation increases with ICP growth, as observed in real infusion tests.

For a better representation of the pre-infusion ICP signal, $p_B(t)$, it is possible to use its Fourier time series. Equation (31) will then have the more general form:

$$p_B(t) = p_{B0} + (p_{B0} - p_0) \left\{ \exp \left[\sum_{k=1}^n \lambda_k \sin(k\omega_1 t + \psi_k) \right] - 1 \right\} \quad (33)$$

where n denotes the number of harmonic components of the pulse and respiratory waves, λ_k and ψ_k , define the amplitudes and the phase angles of each component.

Accordingly, the formula (30) describing ICP growth during the IT will take the final form:

$$p(t) \approx p_0 + \frac{(p_{B0} - p_0)(p'_{B0} - p_0) \cdot \exp \left[\sum_{k=1}^n \lambda_k \sin(k\omega_1 t + \psi_k) \right]}{(p_{B0} - p_0) + (p'_{B0} - p_{B0}) \exp \left[-\frac{EQ_i(p'_{B0} - p_0)}{(p'_{B0} - p_{B0})} t \right]} \quad (34)$$

The above expression will be applied to simulate an “ideal”, infusion test curve for each individual patient.

Validation of the model

It is very difficult to estimate *a priori* the order of magnitude of both coefficients of pulsation γ_1 and γ_2 to check, whether their values remain small during IT. It is so, because we know neither the value of compliance of arterial wall, nor the amplitude of pulsation of the sagittal sinus pressure. We can only speculate, that under the physiological respiration, the amplitude of the pressure pulsation in the airways is close to the value of p_{SSO} (ca 7.7 mmHg) and varies around a mean value of 10 mm of Hg. During the mechanical ventilation, this amplitude rarely exceed 30 mm Hg. For the typical range of respiration frequency (10-16 breaths/min), the angular frequency remains within the range 60 to 100 [rad/min]. Assuming the value of resistance of reabsorption to be of order of tens (in hydrocephalic patients R is usually higher than 12 mmHg/ml/min), the value of γ_2 can be estimated to be approximately 0.01, so much less than 1.

Also we do not know whether assumptions of constancy of cerebral blood volume and constancy of the average sagittal sinus pressure during infusion, being the principles of the original Marmarou model, are fulfilled. Increase of ICP may lead to decrease of cerebral perfusion pressure followed by an increase of the volume of arterial bed, decrease of its resistance and increase of pressure in vessels giving origin to venous bed and in veins (also in superior sagittal sinus).

Therefore, to check whether the proposed, simple analytical model of IT may be applied in practice, we analyzed 25 infusion tests that were obtained during routine diagnostic procedures with hydrocephalic patients in the Neurosurgical Clinic of the Jagiellonian University. In all cases, the lumbar infusion test (IT) was performed using one puncture needle, with an infusion rate $Q_i = 2$ ml/min. Due to application of only one needle there is a step increase in pressure after infusion, causing a systematic error in the ICP measurement. This error was compensated. The sampling frequency of the pressure signal, measured with a piezoelectric transducer, was 20 Hz. A detailed description of the conditions in which the infusion tests were performed is contained in [8].

Before starting each IT, the measurement system performs an evaluation of the frequency spectrum of the patient's resting (baseline) pressure. Based on this evaluation, the angular frequencies, ω_k , the harmonic amplitudes, A_k and the phases, ψ_k , of the pulse and respiratory-related pressure waves were determined. The measured intracranial pressure, $ICP(t)$, as well as the CSF pulse pressure, AMP , during infusion test, were approximated using Marmarou's model. The former by the relation $p_M(t)$, given by (32), the latter, by the well known, linear relation

$$AMP = k(p - p_0) \quad (35)$$

To identify the individual parameters of ICP dynamics: R , E and p_0 , a unique, in-house computer software based on the Nelder-Mead optimization algorithm was used [20]. The values of pulsation coefficients λ_k , were then calculated from the formula (36) (resulting directly from (33)), shown below:

$$\lambda_k = \frac{A_k}{(p_{B0} - p_0)} \quad (36)$$

Finally, basing on equation (34), the simulated course, $p(t)$, of the IT was obtained.

Results

Figures 3a and 4a match a fragment of the baseline pressure signal of two exemplary ICP infusion tests to their Fourier time series composed of the main vascular and respiratory harmonics shown in details in figures 3b and 4b. Figures 3c,d and 4c,d compare the real infusion tests curves with their simulated results. The individual values of Marmarou's model parameters, as well as the values of pulsation coefficients, λ_k , used in modeling are displayed in the relevant drawings. One patient from each group, with dominating arterial or respiratory component, was chosen.

The mean values of all calculated parameters of ICP dynamics as well as the mean values of the first and the second harmonic of coefficients of vascular pulsation (denoted by γ_{11} and γ_{12}) and respiratory pulsations (denoted by γ_{21} and γ_{22}) are set up in Table 1.

In 9 patients (36%) the resistance to CSF outflow was normal, that is lower than 10 mmHg/ml/min [2], 14 patients have R greater than 12 mmHg/ml/min, usually treated as the threshold value for the candidates for shunting [12], the remaining 2

Table 1. Average parameters of ICP dynamics of 25 investigated patients.

Parameter	Mean $\pm$ SD	Min	Max
Baseline pressure, p_{B0} [mmHg]	10.8 ± 5.3	2.3	23.8
Resistance of CSF reabsorption, R [mmHg/ml/min]	12.9 ± 6.7	7.0	35.2
Cerebral elasticity, E [1/ml]	0.184 ± 0.08	0.09	0.353
Reference pressure, p_0 [mmHg]	6.6 ± 4.6	0.1	16.2
Coefficient of first harmonic of vascular pulsation, γ_{11}	0.095 ± 0.062	0.006	0.250
Coefficient of second harmonic of vascular pulsation, γ_{12}	0.031 ± 0.021	0.000	0.108
Coefficient of first harmonic of respiratory pulsation, γ_{21}	0.043 ± 0.032	0.006	0.126
Coefficient of second harmonic of respiratory pulsation, γ_{22}	0.018 ± 0.018	0.000	0.070

patients have R between 8 and 12 mmHg/ml/min. In 12 patients (48%) the cerebral elasticity E (which is inversely proportional to the pressure/volume index $PVI \approx 2.303/E$) remained within the norm (0.05-0.18 1/ml) [10]. The rest of the patients have cerebral elasticity elevated above the upper limit.

In 20 patients (80%) the values of coefficient of the vascular pulsation, γ_{11} , were lower than 0.1, the remaining 5 patients had values between 0.1 and 0.25. As far as the values of coefficient of the respiratory pulsation, γ_{21} , are concerned, they were lower than 0.1 in most tests, with exception of only 2 cases that exceeded this limit slightly.

Figure 3a. A fragment of the registered and simulated baseline pressure of patient “A”.

Figure 3b. Frequency spectrum of the baseline pressure – arrows indicate harmonic components of ICP waves taken into consideration.

Figure 3c. ICP growth during IT of patient "A". Continuous line represents the approximation of IT by Marmarou model.

Figure 3d. Simulated ICP growth based on derived equation (34).

Figure 4a. A fragment of the registered and simulated baseline pressure of patient “B”.

Figure 4b. Frequency spectrum of the baseline pressure – arrows indicate harmonic components of ICP waves taken into consideration.

Figure 4c. ICP growth during IT of patient "B". Continuous line represents the approximation of IT by Marmarou model.

Figure 4d. Simulated ICP growth based on derived equation (34).

Discussion

The present study demonstrates that complicated pulsation and growth in intracranial pressure during infusion test can be successfully modeled by the relatively simple analytical expression (34), which was derived in this paper. Possible explanations of this conclusion are:

- the values of the coefficients of pulsation were in each test sufficiently small to fulfill assumptions of the proposed approximate solution;
- simplifications of the original Marmarou's model were fulfilled, namely:
 - active changes in the cerebral blood volume that might occur during IT may be disregarded,
 - the parameters of intracranial dynamics (R, E, p_0) may be assumed constant,
 - heart frequency changes related to respiration [18] were negligible.

Most opinions of clinical importance of the three parameters of the Marmarou's model arrange them in the following order: R, E, p_0 . So far, the resistance to CSF reabsorption, R , has gained significant evidence of prognostic value [5], despite ongoing discussion on age dependence of upper physiological limits. That is so, because elevation of R is not always correlated with a good outcome after shunting, particularly in NPH of the elderly patients. Still more controversy concerns clinical meaning of elastance coefficient, E . In some clinical investigations [25], elevated elasticity ($E > 0.18$) is considered as a poor pressure-volume compensatory reserve, whereas its lowest values ($E < 0.08$) may indicate brain atrophy with a very compliant CSF system. The physiological meaning of the last parameter – the reference pressure, p_0 , is obscure and its range of change, not known. By some authors p_0 is treated as the average pressure in the venous compartment and may be equal to p_{SS0} . The others assume that this variable may be neglected [17].

Our practice indicates that the reference pressure, p_0 , plays an important role in obtaining good correlation between real and the simulated IT curve. Firstly, because its value determines the degree of pulsation amplitude growth during infusion, M , which is given by the relation (37), given below and is depicted qualitatively in Fig. 5

$$M = \frac{AMP(p'_{B0})}{AMP(p_{B0})} = \frac{(p'_{B0} - p_0)}{(p_{B0} - p_0)} = \frac{\left(\frac{p'_{B0}}{p_{B0}} - \frac{p_0}{p_{B0}} \right)}{\left(1 - \frac{p_0}{p_{B0}} \right)} \quad (37)$$

Figure 5. Coefficient of pulsation growth, M , during infusion vs relative reference pressure, p_0/p_{B0} .

We can see, that when p_0 approaches the value of baseline pressure, p_{B0} , the pulsation amplitude growth becomes unrealistically high (theoretically it tends to infinity).

Secondly, the value of reference pressure is coupled with a value of elastance coefficient via the definition of cerebral compliance, $C(p)$ (see eq (4)). It means that these parameters are not linearly independent. For example, initial brain compliance, $C(p_{B0})$ may be described by an infinite number of pairs of values (E_i, p_{0i}) satisfying relation (38):

$$C(p_{B0}) = \frac{1}{E_i(p_{B0} - p_{0i})} = \text{const} \quad (38)$$

From the above expression it follows that the smaller the difference between baseline and reference pressure, the greater the value of elastance coefficient. Some other consequences of the dependence between E and p_0 were mentioned elsewhere [8, 9].

For solving this problem, at first the value of the reference pressure, p_0 , was estimated using the characteristics of the AMP vs. p , given by (35). Then the individual

parameters of the intracranial pressure dynamics, (R, E, p_0) , were established, using p_0 values close to the previously obtained value. A much better adjustment was obtained not only in IT trend (which was described by means of the original Marmarou model), but also in the actual increase of AMP.

In order to examine the correctness of the used algorithm of identification of the Marmarou model parameters, the artificially generated tests were used. They were made with the help of the equation (12), calculated for arbitrary values of the intracranial compensation parameters (R, E, p_0) , and the arbitrary amplitudes and the phases of the pulsating elements. In all cases, the discrepancy between calculated (R', E', p'_0) and assumed parameters did not exceed 1%.

Conclusion

As mentioned in the introduction, it was not our goal to create a model of IT curve which can simulate all facets of the living system, but simply to improve the well established Marmarou's model by adding the pulsatile components. The relatively simple analytical formula, derived in this paper, serves this purpose very well and enables to model complicated behavior of the pulsation and growth in intracranial pressure during infusion.

The simulation of infusion curve which was based on the proposed equation (34) makes possible more exact analysis of the parameters of intracranial pressure. This method designates much more exactly the value of the reference pressure, which is usually treated as a secondary and of uncertain significance. In our opinion, the properly identified value of the reference pressure decides on the degree of AMP growth during IT, as well as on the E value, which is sometime used as a prognostic factor in shunting of hydrocephalic patients.

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References

- [1] Agarval G, Berman B, Stark L. A Lumped Parameter Model of the Cerebrospinal System IEEE Trans Biomed Eng BME 1969; 16: 45-53.
- [2] Albeck MJ, Borgesen SE, Gjerris F, Schnidt JF, Sorensen PS. Intracranial pressure and cerebrospinal fluid outflow conductances in healthy subjects. J Neurourg 1991; 74: 597-600.
- [3] Avezaat CJJ, Eijndhoven JHM. Cerebrospinal fluid pulse pressure and craniospinal dynamics. A theoretical, Clinical and experimental study (thesis) Hague: A Jongbloed en Zoon. (1984).
- [4] Balestri M, Czosnyka M, Steiner L A, Schmidt E, Smielewski P, Matta B, Pickard JD. Intracranial hypertension: what additional information can be derived from ICP waveform after head injury? Acta Neurochir. (Wien) 2004; 146: 131-141.
- [5] Boon AJW, Tans JTh, Delwel EJ, Egeler-Peerdeman SM, Hermans J. The Dutch Normal-Pressure Hydrocephalus Study How to select patients for shunting? An analysis of four diagnostic criteria. Surg Neurol 2000; 53: 201-207.
- [6] Bearing HA. Choroid plexus and arterial pulsations of cerebrospinal fluid: demonstration of the choroid plexus as a cerebrospinal fluid pump. Arch. Neurol. Psychiatry 1955; 73: 165-173.
- [7] Chop M, Portnoy HD. Systems analysis of intracranial pressure. J Neurosurgery 1980; 53: 516-527.
- [8] Cieřlicki K, Czepko R. Optimal use of the lumbar infusion test in patients with communicating hydrocephalus. Theoretical considerations in comparison to clinical observation. Neurol Neurochir Pol 2004; 38: 189-195.
- [9] Cieřlicki K, Czepko R, Libionka W. Comments on "Analysis of intracranial pressure during and after the infusion test in patients with communicating hydrocephalus". Physiol Meas 2006; 27: L5-L8.
- [10] Czosnyka M, Barorski L, Roszkowski M, et al. Cerebrospinal compensation in hydrocephalic children. Child's Nerv System 1993; 9: 17-22.
- [11] Czosnyka M. Analiza dynamicznych procesów wewnątrzczaszkowej kompensacji objętościowej. Prace Naukowe „Elektronika” z. 111, Oficyna Wydawnicza PW, Warszawa (1996).
- [12] Delwel EJ, de Jonge DA, Avezaat CJJ. The prognostic value of clinical characteristics and parameters of cerebrospinal fluid hydrodynamics in shunting for idiopathic normal pressure hydrocephalus. Acta Neurochir (Wien) 2005; 147: 1037-1043.
- [13] Duros J, Nadvornik P. Investigation of cerebral blood circulation on computer model J Neurosurg Sc 1977; 21: 243-246.
- [14] Giulioni M, Ursino M. Impact of cerebral perfusion pressure and autoregulation on intracranial dynamics: A modeling study. Neurosurgery 1996; 39: 1005-1015.

- [15] Juniewicz H, Kasproicz M, Czosnyka M, Czosnyka Z, Gilewski S, Dzik M and Piccard JD. Analysis of intracranial pressure during and after the infusion test in patients with communicating hydrocephalus. *Physiol Meas* 2005; 26: 1039–1048.
- [16] Lakin W, Stevans SA, Tranmer BI, Penar PL. A whole body mathematical model for intracranial pressure dynamics. *J Math Biol* 2003; 46: 347-383.
- [17] Marmarou A, Shulman K, Rosende RM. A nonlinear analysis of the cerebrospinal fluid system and intracranial pressure dynamics. *J Neurosurg* 1978; 48: 332-344.
- [18] Morgalla MH, Stumm F, Hesse G. A computer-based method for continuous single pulse analysis of intracranial pressure waves *J Neurol Sc* 1999; 168: 90-95.
- [19] Murphy GM. Ordinary Differential Equations and their Solutions. Van Nostrand Co Inc, New York (1960).
- [20] Nelder JA, Mead R. A Simplex Method for Function Minimization. *Computer J* 1965; 7: 308-313.
- [21] Piechnik S, Czosnyka M, Harris NG, Minhas PS, and Pickard JD. A model of the cerebral and CSF circulations to examine the asymmetry in cerebrovascular reactivity. *J Cerebral Blood Flow and Metabolism* 2001; 21: 182-192.
- [22] Sorek S, Bear J, Karni Z. A non-steady compartmental flow model of the cerebrovascular system. *J Biomech* 1988; 21: 695-704.
- [23] Sorek S, Bear J, Karni Z. Resistances and compliances of a compartmental model of the cerebrovascular system. *Ann Biomed Eng* 1989; 17: 1-12.
- [24] Schmidt B, Schwartz JJ, Czosnyka M, Sander D, Wittich I, Klingelhoefer J. A method for a simulation of continuous intracranial pressure curves. *Comput Biomed Res* 1998; 31: 231-243.
- [25] Szewczykowski J, Śliwka S, Kunicki A, et.al. A fast method of estimating the elastance of the intracranial system. *J Neurosurgery* 1978; 47: 19-26.
- [26] Takemae TY, Kosugi J, Ikebe Y, Kumagai K, Matsuyama N, Saito H. A Simulation Study of Intracranial Pressure Increment Using an Electrical Circuit Model of Cerebral Circulation *IEEE Trans Biomed Eng (BME)* 1987; 34: 958-962.
- [27] Ursino M. A mathematical study of human intracranial hydrodynamics, Part I The cerebrospinal fluid pulse pressure. *Ann Biomed Eng* 1988; 16: 379-401.
- [28] Ursino M, Lodi CA. A simple mathematical model of the interaction between intracranial pressure and cerebral hemodynamics. *J Appl Physiol* 1997; 82: 1256-1269.