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CSF dynamic analysis of a predictive pulsatility-based infusion test for Normal Pressure Hydrocephalus

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ABSTRACT

Introduction

Disturbed cerebrospinal fluid (CSF) dynamics are part of the pathophysiology of Normal pressure hydrocephalus and can be modified and treated with shunt surgery. This study investigated the contribution of established CSF dynamic parameters to AMP_{mean}, a prognostic variable defined as mean amplitude of cardiac-related intracranial pressure pulsations during 10 minutes of lumbar constant infusion, with the aim of clarifying the physiological interpretation of the variable.

Method

AMP_{mean} and CSF dynamic parameters were determined from infusion tests performed on 18 patients with suspected NPH. Using a mathematical model of CSF dynamics an expression for AMP_{mean} was derived and the influence of the different parameters was assessed.

Results

There was high correlation between modelled and measured AMP_{mean} ($r=0.98$, $p<0.01$). Outflow resistance and three parameters relating to compliance were identified from the model. Correlation analysis of patient data confirmed the effect of the parameters on AMP_{mean} (Spearman's $\rho=0.58-0.88$, $p<0.05$). Simulated variations of ± 1 SD of the parameters resulted in AMP_{mean} changes of 0.6-2.9 SD, with the elastance coefficient showing the strongest influence.

Conclusion

Parameters relating to compliance showed the largest contribution to AMP_{mean}, which supports the importance of the compliance aspect of CSF dynamics for the understanding of the pathophysiology of NPH.

Keywords: cerebrospinal fluid dynamics; prognostic tests; intracranial pressure; hydrocephalus, normal pressure

Introduction

The cerebrospinal fluid (CSF) surrounds the brain and spinal cord and fills the cerebral ventricles. Conventional knowledge posits that CSF is formed continually in the ventricles and circulates from there to the subarachnoid space surrounding the brain and spine before being absorbed into venous blood through structures called arachnoid granulations mainly located in the intracranial subarachnoid space[30, 34]. The relationships describing the interactions of the volume and flow of CSF and the intracranial pressure (ICP) are referred to as the CSF dynamics. Within the rigid confines of the skull there is a limited amount of space and in accordance with the Monro-Kellie doctrine any increase in the volume of brain matter, blood or CSF must be compensated for by an equal decrease in the other volumes.[28] This leads to an interaction between the CSF dynamics and the hemodynamics, which is illustrated by the occurrence of ICP pulsations at the cardiac frequency caused by the transient increase of intracranial arterial blood occurring with each heart beat. To compensate for the increase venous blood is forced from the intracranial space, leading to pulsatile venous outflow, and CSF is forced into the spinal subarachnoid space, leading to oscillating flows within the CSF system.[19] The pulse amplitude of the ICP pulsations will depend on the compliance of the system (C) which, along with the outflow resistance of CSF (R_{out}), is a major aspect of the CSF dynamics.

Normal pressure hydrocephalus (NPH) is a condition with enlarged cerebral ventricles and symptoms of gait/balance disturbance, cognitive decline, and urinary incontinence. The ventricular enlargement is believed to relate to a disturbance of the CSF dynamics, though the nature of the disturbance, i.e. the pathophysiology, is not fully elucidated. NPH can be successfully treated with a surgically implanted shunt, which drains excess CSF from the ventricles. However, not all patients improve, and as shunt surgery is expensive and may cause complications, prognostic tests are commonly performed, but different centres employ different tests and most of them are subject to conflicting findings in the scientific literature[26]. One approach to prognostic testing is to investigate the CSF dynamics by an infusion test, where ICP is measured during externally controlled infusion of artificial CSF. Traditionally these tests are used to assess R_{out} , which is relatively straightforward to estimate and is specifically reduced by the insertion of a shunt in the system. More recently suggested prognostic tests often focus on parameters describing the cardiac-related pulsations in ICP or CSF flow.[5, 10, 17, 31, 33] So far no consensus on the most appropriate test has been reached, and the interaction of different CSF dynamic parameters complicates the effort of identifying the key aspect of the CSF dynamic disturbance. One test with promising results is based on the mean pulse amplitude of cardiac-related ICP pulsations (AMP_{mean}) during 10 minutes of constant flow infusion.[16] The test was empirically derived as the best prognostic test based on pulse amplitude (AMP) assessed during lumbar infusion tests. The suggested critical threshold for AMP_{mean} is different than that of AMP assessed during overnight monitoring, but the two tests should depend on the same patient specific CSF dynamic parameters.

The ICP response during constant infusion is determined by a number of different parameters of the CSF dynamics (see table 1). As AMP is dependent on ICP level,

AMP_{mean} is therefore also dependent on these parameters. In order to clarify the physiological interpretation of the prognostic test it is worthwhile to analyze the contributing CSF dynamics further. Investigating the interactions between the CSF dynamic parameters affecting the prognostic testing may reveal a common aspect shared by several investigated prognostic tests, which is thus of interest for further research into pathophysiology and treatment of NPH. This study therefore aimed to assess the contribution of different CSF dynamic parameters to AMP_{mean} using simulations and correlation analysis based on an established mathematical model of the CSF dynamics and pressure and flow data from patients investigated for NPH with an advanced infusion technique.

Methods

The process for determining which CSF dynamic parameters influence the suggested test parameter AMP_{mean} , and how strongly each of these parameters affect the value of AMP_{mean} , can be described in three steps:

1. Estimation of the expected variation of values within a suspected NPH population by determination of mean and standard deviation (SD) for AMP_{mean} and all parameters of CSF dynamics measurable via infusion test in a group of NPH patients.
2. Derivation of a theoretical expression for AMP_{mean} from the established mathematical model of the CSF dynamics that is used in infusion investigations.
3. Assessment of the influence of identified CSF dynamic parameters on the test parameter, AMP_{mean} , by analysing the changes in AMP_{mean} resulting from variation in each parameter while keeping the other parameters constant.

The parameters of the model are listed and explained in table 1.

Table 1: List of CSF dynamic parameters.

Parameter name / abbreviation	Explanation
R_{out}	Resistance to outflow of CSF from the system [$kPa\ ml^{-1}\ min^{-1}$]
C	Compliance of the craniospinal system (inverse of elastance) [ml/kPa]
k	Elastance coefficient of the craniospinal system, pressure independent parameter determining compliance [ml^{-1}]
ICP_r	Baseline or resting intracranial pressure (ICP) [kPa]
P_o	Pressure constant of the mathematical model, extrapolated to pressure at infinite compliance [kPa]
$ICP_r - P_o$	Distance of baseline intracranial pressure to pressure at infinite compliance, determines compliance at baseline [kPa]
ΔV	Transient volume increase of intracranial arteries associated with each cardiac cycle [ml]
RPPC	Relative pulse pressure coefficient, slope of linear relationship between amplitude and mean ICP, $RPPC = (e^{k\Delta V} - 1)$
AMP_{mean}	Mean pulse amplitude of cardiac-related ICP pulsations during 10 minutes of constant infusion at a rate of 1.5 ml/min [kPa]

Physiological description of the CSF system

The CSF system consists of the four cerebral ventricles (within the brain) and the intracranial and spinal subarachnoid space (which surrounds the brain and spinal cord, respectively). The ventricles are connected to each other and to the subarachnoid space through narrow openings and passages, and thus the system is communicating through the geometry of the anatomy is complicated. The established knowledge describes that CSF is secreted from the choroid plexus in the ventricles[34], and mainly absorbed to venous blood through arachnoid granulations in the subarachnoid space[13]. This knowledge has however been questioned as new methods, mostly in magnetic resonance (MR) imaging, have been developed which can assess local flows in the system. Alternative or additional pathways for CSF absorption via cranial nerve roots to the lymphatic system, as well as both secretion from and absorption to the capillaries and the interstitial fluid of the brain have been described.[29, 30]

The ventricles and part of the subarachnoid space is contained within the rigid confines of the skull, and thus interacts intimately with the arterial and venous systems through the fixed total volume these systems can inhabit. The Monroe-Kellie doctrine states that any increase in the volume of brain matter, blood or CSF must be compensated for by an equal decrease in the other volumes.[28] As brain matter is essentially incompressible, and the pressure in the arterial system exceeds that in the CSF or venous system, the normal compensatory shift of volume stems from venous blood and CSF. For a slow expansion increasing amounts of CSF can be absorbed, reducing the total CSF volume. In response to more rapid volume increases however, such as the small transient volume increase of intracranial arteries which occurs with each cardiac cycle, CSF is not absorbed but redistributed from the intracranial compartment of the CSF system to the spinal compartment. Along with this oscillatory shift of CSF volume between compartments, small amounts of venous blood are also shifted to extracranial veins, causing pulsatile intracranial venous outflow.[19] This ability to shift CSF and venous blood from the intracranial space and thus dampen the pressure increase caused by the increased arterial blood volume, or any other active change of craniospinal volume, is what we refer to as compliance of the craniospinal system.[36] The easier it is to shift these volumes, and the more volume that can be displaced, the higher the compliance. Thus, the pulsatility of both arterial and venous blood flow, as well as CSF flow have potential impact on the ICP pulse amplitude, which has been highlighted by several authors.[8, 19, 20, 22, 35, 36]

Modelling the CSF dynamics

ICP is a function of the volume of CSF, thus the change in ICP over time depends on the change in volume:

$$\frac{dICP}{dt} = \frac{dICP}{dV} \frac{dV}{dt}. \quad (1)$$

The derivative of ICP with respect to volume is the elastance of the system, the inverse of which is compliance (C)[18]. According to an established mathematical

model of the CSF dynamics[25] the relationship between ICP and volume is exponential, and compliance can be described as:

$$C = \frac{dV}{dICP} = \frac{1}{k(ICP - P_0)}. \quad (2)$$

The term k is called the elastance coefficient. The constant term P_0 was introduced by Avezaat and van Eijndhoven[7] to improve the fit of the model to experimental data; it corresponds to the pressure where compliance is infinite. The physiological interpretation of P_0 was suggested to relate to venous pressure but this has not been confirmed.[6, 7] Equations (1) and (2) leads to:

$$\frac{dICP}{dt} = k(ICP - P_0) \frac{dV}{dt}. \quad (3)$$

The volume change over time in the CSF system depends on the formation of new CSF (I_f), the absorption of CSF (I_a), and external infusion of artificial CSF (I_{ext}). The so called Davson equation describes absorption of CSF as a function of ICP, the resistance to CSF outflow (R_{out}) and the pressure in the dural venous sinus (P_d)[15]:

$$I_a = \frac{ICP - P_d}{R_{out}}. \quad (4)$$

At baseline, or resting pressure (ICP_r), the system is at equilibrium and thus absorption and formation must be equal. As formation is generally considered pressure independent[4, 18] this means that equation (3) can be rewritten (see Appendix) as:

$$\frac{dICP}{dt} = \frac{k(ICP - P_0)}{R_{out}} (ICP_r - ICP + R_{out} I_{ext}). \quad (5)$$

With the assumption of $I_{ext} = \text{constant}$, which is true for constant infusion, equation (5) can be solved using the variable substitution $x = 1/(ICP - P_0)$, and the integrating factor method (see Appendix). The result is an expression of ICP as a function of time. If the infusion is assumed to start at ICP_{start} ($ICP(0) = ICP_{start}$), the following expression is derived:

$$ICP(t) = \frac{(R_{out} I_{ext} + ICP_r - P_0)(ICP_{start} - P_0)}{ICP_{start} - P_0 + (R_{out} I_{ext} + ICP_r - ICP_{start}) e^{-tk(I_{ext} + (ICP_r - P_0)/R_{out})}} + P_0. \quad (6)$$

The mean ICP (ICP_{mean}) for a time interval T starting at the beginning of infusion can be calculated using integration as:

$$ICP_{mean} = \frac{1}{T} \int_0^T ICP dt = \frac{1}{T} \int_0^T \frac{(R_{out} I_{ext} + ICP_r - P_0)(ICP_{start} - P_0)}{ICP_{start} - P_0 + (R_{out} I_{ext} + ICP_r - ICP_{start}) e^{-tk(I_{ext} + (ICP_r - P_0)/R_{out})}} dt + \frac{1}{T} \int_0^T P_0 dt. \quad (7)$$

The second term of equation (7) results in P_0 , while the first term can be rewritten as:

$$\frac{1}{T} \int_0^T \frac{(R_{out}I_{ext} + ICP_r - P_0)(ICP_{start} - P_0)e^{Tk(I_{ext} + (ICP_r - P_0)/R_{out})}}{R_{out}I_{ext} + ICP_r - ICP_{start} + (ICP_{start} - P_0)e^{Tk(I_{ext} + (ICP_r - P_0)/R_{out})}} dt. \quad (8)$$

In this equation the term $(R_{out}I_{ext} + ICP_r - P_0)(ICP_{start} - P_0)$ can be broken out of the integral, which can then be calculated using the formula:

$$\int \frac{e^{at}}{b + ce^{at}} dt = \frac{1}{ac} \ln(b + ce^{at}) \quad (9)$$

with $a = k(I_{ext} + (ICP_r - P_0)/R_{out})$, $b = (R_{out}I_{ext} + ICP_r - ICP_{start})$ and $c = (ICP_{start} - P_0)$. The resulting expression for ICP_{mean} then becomes:

$$ICP_{mean} = \frac{R_{out}}{Tk} \ln \left(\frac{R_{out}I_{ext} + ICP_r - ICP_{start} + (ICP_{start} - P_0)e^{Tk(I_{ext} + (ICP_r - P_0)/R_{out})}}{R_{out}I_{ext} + ICP_r - P_0} \right) + P_0. \quad (10)$$

When AMP_{mean} is used for outcome prediction in NPH the infusion is initiated at baseline ICP ($ICP_{start} = ICP_r$) and thus equation (6) can be simplified to:

$$ICP_{mean} = \frac{R_{out}}{Tk} \ln \left(\frac{I_{ext} + (ICP_r - P_0)e^{Tk(I_{ext} + (ICP_r - P_0)/R_{out})}}{I_{ext} + (ICP_r - P_0)/R_{out}} \right) + P_0. \quad (11)$$

The CSF dynamic model [7, 25] can also be used to derive an expression for pulse amplitude (AMP) as a function of ICP:

$$AMP = (e^{k\Delta V} - 1)(ICP - P_0). \quad (12)$$

Here ΔV is an instantaneous volume increase, which corresponds to the systolic expansion of the intracranial arteries associated with each cardiac cycle, rather than a volume variation of CSF. However, since the total intracranial volume is fixed, an increase in the intracranial volume of blood reduces the space available for CSF, which has the same affect on ICP as an increase of the CSF volume. Both ΔV and the elastance coefficient (k) are assumed to be ICP independent, which makes AMP a linear function of ICP.[21, 36] The term RPPC (relative pulse pressure coefficient) is defined as the linear coefficient of the equation, i.e. $(e^{k\Delta V} - 1)$. [21] Thus the output from the prognostic test, mean AMP over the interval T (AMP_{mean}), can be described in terms of CSF dynamic parameters as:

$$AMP_{mean} = RPPC(ICP_{mean} - P_0). \quad (13)$$

Clinical data

The data from infusion investigations of 18 patients with idiopathic or secondary NPH (6 F/12 M, mean age 76 ± 5 years, range 67-82 years) where the prognostic protocol included a constant infusion test ($I_{ext} = 1.5$ ml/min) was re-examined. During the investigations lumbar CSF pressure was measured, first at rest (15-20 min) and then during constant infusion at a rate of ca 1.5 ml/min, lasting at least 10 minutes. The earliest investigations were performed with an in-house developed automated

infusion apparatus[3, 24] and the later investigations with the commercial version of the apparatus, CELDA (Likvor AB, Umeå, Sweden)[32].

Data analysis

A value of mean ICP and AMP was determined for each 1.5 second interval of the 100 Hz sampled data. AMP values were calculated as the difference between the maximum and the minimum values of high-pass filtered ICP (digital zero-phase filtering using a 5th order Butterworth filter with a cut-off frequency of 0.5 Hz). The values of the last 5 minutes of the baseline registration were averaged to determine ICP_r and AMP_r . The values from the first 10 minutes of constant infusion were averaged to determine ICP_{mean} and AMP_{mean} .

The values of mean ICP (sampled during infusion) between $ICP_r + 0.4$ kPa and 4.4 kPa were sorted according to magnitude, AMP values were sorted according to their corresponding ICP. Median values of ICP and AMP were determined for each consecutive set of five values. The median values were then used in the linear regression with AMP as the dependent variable to determine values of RPPC and P_o . In accordance with equation (12) $RPPC = (e^{k\Delta V} - 1)$ is the slope of the regression line and P_o the intercept with the ICP axis (Figure 1).

Fig. 1 A constant flow infusion (light gray: original data, dark grey: averaged to 1 value/s) with the fitted curve (black) from the estimation of R_{out} and k (left panel) and the AMP versus ICP curve (grey circles) for the same patient with the regression line (black) used to estimate RPPC (=slope) and P_o (=intercept with ICP-axis) (right panel)

Values of R_{out} and k were determined by fitting the theoretical expression for ICP to measurement data using unconstrained nonlinear optimization based on the Nelder-Mead Simplex method (the “fminsearch” algorithm of MATLAB, version 7.4.0, MathWorks Inc., Natick, MA, USA). For this analysis the 100 Hz data was averaged into 1 ICP value per second. The expression used was equation (6) with ICP_{start} set to the mean ICP of the last 10 seconds before the start of infusion (rather than ICP_r

which was used for the AMP_{mean} calculation). The estimated P_o was used as an input to the expression. Initial guesses for the value of k were based on the individual estimated RPPC values and a ΔV of 2 ml (from literature)[36], the initial guess for R_{out} was 0.1 kPa ml⁻¹ min⁻¹ for all patients. Mean and SD for the 18 patients were determined for all parameters. An example of an investigation with the fitted expression, as well as the corresponding plot of AMP versus ICP with the linear regression, is shown in figure 1.

Limitations of the CSF dynamic model

The CSF dynamic model is not valid at low ICP levels [11, 31], which will affect the infusion test analysis for patients where data is collected below this pressure. In this study the infusion phase was started at an ICP outside the model range in one patient (see figure 2). It can be observed that the values in the AMP versus ICP curve deviate from the line below approximately 1.5 kPa, at these pressures the CSF dynamic model is not valid. The low starting pressure was due to ICP reduction from ICP_r caused by CSF sampling for biochemical analysis. In this case the data collected below the limit was simply excluded in the estimation of all CSF dynamic parameters except AMP_{mean} , which was always determined from the first 10 minutes of infusion in accordance with the prognostic test. Another patient had ICP_r below the estimated P_o , which is outside the scope of the model since $ICP=P_o$ would correspond to infinite compliance. All parameters were in this case approximately estimated by setting P_o to $ICP_r-0.3$ kPa[2].

Fig 2. AMP versus ICP curve (grey circles) for a patient where data was sampled outside the valid range of the mathematical model as evidenced by the values deviating from the regression line (black) below approximately 1.5 kPa

Assumptions of the CSF dynamic model

The mathematical model of the CSF system used in this study is well established, particularly for use with data from infusion investigations.[11, 18, 25]. It is a lumped

model, and thus the sites of secretion and absorption are not specifically modelled. Some assumptions about these mechanisms are however made. Absorption of CSF (I_a) is assumed to be dependent on R_{out} , and the difference in pressure between the CSF system and the dural venous sinuses (equation (4)).[13-15] CSF absorption and formation (I_f) are furthermore assumed to be equal at baseline (equation (5), Appendix: equation (16)). This assumption is based on the observation that the volume of CSF is normally stable over time, which requires that no more CSF is secreted than is absorbed or the CSF volume would expand critically. Finally, R_{out} , P_d and I_f are all assumed to be ICP independent (equations (4-5), Appendix: equation (16)) which, along with the previous assumptions, means that CSF absorption can be described as a linear function of the increase in ICP above baseline, with R_{out} as the slope. This relationship has previously been verified in relation to R_{out} estimation.[1, 4]

The mathematical model was originally designed to describe slower changes in the volume and pressure of the CSF system, such as those occurring with infusion. However, the derivation of the expression for AMP (equation (12)) was made soon after the model was first presented, and has been validated for a wide range of ICP in both animals and humans.[6, 7, 21, 31] The expression simplifies the transient volume increase of arterial blood as a small instantaneous volume increase, ΔV . In the definition of RPPC, ΔV is assumed to be independent of ICP and constant during periods of rest corresponding to the duration of an infusion investigation.[21] This assumption leads to the linearity of equation (13), which has been verified in several studies and is used to determine the range of ICP where the model is valid.[6, 7, 21, 31]

Validation of the CSF dynamic model

To validate that the mathematical model was applicable for description of AMP_{mean} the measured patient values of AMP_{mean} were compared with theoretical values based on the model. The theoretical values were calculated with $ICP(o)$ set to the mean ICP of the last 10 seconds before the start of infusion, and I_{ext} set to the mean flow during the first 10 minutes of infusion, to best correspond to the actual experimental circumstances. Theoretical and measured values were compared using a paired samples Student's t-test and a linear correlation coefficient (Pearson's correlation coefficient). A good agreement between measured and theoretically calculated AMP_{mean} supports that equations (6) and (12) were valid descriptions of the dynamics of the CSF system.

A non-parametric partial correlation analysis was also performed to confirm if the measured values of the different parameters identified as affecting AMP_{mean} in the theoretical expression correlated to the measured AMP_{mean} from the clinical data. This analysis consisted of the calculation of Spearman's ρ (rank correlation coefficient) for each identified and measured parameter in relation to AMP_{mean} , while correcting for the other parameters (partial correlation). A rank correlation coefficient was chosen as the theoretical expression implies that the relationship between the parameters was nonlinear. Partial correlation was used to compensate

for any potential correlation between the different investigated parameters (apart from AMP_{mean})

Assessment of CSF dynamic parameter influence

The theoretical expression and the model validation revealed which parameters should influence the value of AMP_{mean} . To analyze which of these parameters held the strongest influence on AMP_{mean} within the observed range of measured values, i.e. the range of values which may be expected when investigating suspected NPH patients, a parameter sensitivity analysis was performed. Using the expression for AMP_{mean} that resulted from the theoretical derivations, and the mean and confidence interval (estimated as $mean \pm 2$ SD) determined from the patient data for each of the relevant parameters, theoretical AMP_{mean} values were calculated. Lilliefors tests for normality of the distributions of the parameters were performed to confirm that the approximation of the confidence intervals was reasonable. The means of all parameters were input into the theoretical expression and a single parameter was then varied from mean-2 SD to mean+2 SD and the result plotted. The total change in AMP_{mean} resulting from a change from mean-SD to mean+SD in the parameter was also determined, and the ratio of this value to the measured SD of AMP_{mean} was calculated. The process was repeated for each measured parameter in the theoretical expression. All calculations were performed using MATLAB (MathWorks Inc., Natick, MA, USA).

Results

Equations (11) and (13) lead to the following theoretical expression for AMP_{mean} :

$$AMP_{mean} = \frac{(e^{k\Delta V} - 1)R_{out}}{Tk} \ln \left(\frac{R_{out}I_{ext} + (ICP_r - P_0)e^{Tk(I_{ext} + (ICP_r - P_0)/R_{out})}}{R_{out}I_{ext} + ICP_r - P_0} \right). \quad (14)$$

Thus, the mean amplitude during constant infusion ($T=10$ min, $I_{ext}=1.5$ ml/min) was a function of several key parameters of CSF dynamics, specifically the terms k , $(ICP_r - P_0)$, R_{out} and $(e^{k\Delta V} - 1)$, which was equivalent to the measurable parameter RPPC.

Table 2 shows the mean and SD of the different parameters determined from the patient data. The parameters could be approximated as normally distributed (Lilliefors tests: $p>0.05$). AMP_{mean} from the clinical data was not significantly different from the theoretical AMP_{mean} (difference = 0.01 ± 0.13 [mean $\pm$ SD], $p=0.70$). The correlation is illustrated in figure 3 ($r = 0.98$, $p<0.01$).

Table 2: Values of CSF dynamic parameters for 18 patients (mean $\pm$ SD).

ICP_r [kPa]	P_0 [kPa]	$(ICP_r - P_0)$ [kPa]	R_{out} [kPa ml ⁻¹ min ⁻¹]	k [ml ⁻¹]	RPPC	AMP_{mean} [kPa]
1.53 $\pm$ 0.32	0.83 $\pm$ 0.36	0.69 $\pm$ 0.35	1.97 $\pm$ 0.62	0.21 $\pm$ 0.08	0.62 $\pm$ 0.19	1.29 $\pm$ 0.62

Corresponding values in traditional units were $R_{out}=14.8\pm4.6$ mmHg ml⁻¹ min⁻¹ and Pressure Volume Index= 12.5 ± 5.2 ml. ($PVI=1/0.434k$)

Fig. 3 Relationship between the modelled and the measured AMP_{mean} (circles) ($r=98$, $p<0.01$) with a line representing equality (grey); the point which deviates most from the line corresponds to the patient with ICP_r below P_o

The results of the partial correlation analysis are presented in table 3. The four parameters identified in equation (13), with $(e^{k\Delta V}-1)$ substituted for RPPC, were significantly correlated to measured AMP_{mean} (using non-parametric partial correlation).

Table 3: Non-parametric partial correlation coefficient (Spearman's ρ) for each of the relevant parameters, while correcting for the other parameters.

R_{out}	k	ICP_r-P_o	RPPC
0.66**	0.58*	0.82**	0.88**

* significant correlation, $p<0.05$, ** $p<0.01$.

The assessment of parameter influence is illustrated in figure 4. The variation of the elastance coefficient had the strongest influence on the value of AMP_{mean} , while (ICP_r-P_o) had intermediate effect and variation of R_{out} showed a weak influence. For a variation of 2 SD (± 1 SD) around the mean value of k , the simulated change of AMP_{mean} was 2.9 SD. The corresponding changes of AMP_{mean} for variations of (ICP_r-P_o) and R_{out} were 1.2 SD and 0.6 SD, respectively. A range of ΔV values was not measured in this study and thus the influence of a corresponding variation on AMP_{mean} was not assessed. In the analysis of influence of the other parameters the value 2.3 ml, calculated from the measured mean values of RPPC and k ($\Delta V = \ln[RPPC+1]/k$), was used.

Fig. 4 Each plot shows the simulated AMP_{mean} (grey) resulting from varying one parameter from mean-2SD to mean+2SD and keeping the others constant at the mean values (from the clinical data), the dashed and dotted lines show mean $\pm$ 2SD of AMP_{mean} from the clinical data

Discussion

Since the AMP_{mean} parameter can be described by the mathematical model, this offers a possibility for assessing how the different CSF dynamic parameters affect the result of the prognostic test, and thus for evaluating which parameters, and subsequently which physiological property, may be most important in determining outcome from shunt surgery in NPH. Four parameters (ICP_r-P_o , R_{out} , k , $e^{k\Delta V}-1$) were identified as relevant for AMP_{mean} in the model (equation (14)) and showed significant partial non-parametric correlation with AMP_{mean} (table 3).

Though the interactions of the different parameters make the equation far from intuitive, it is possible to understand the basic principles of how the different parameters affect AMP_{mean} . Firstly, three parameters influence ICP_{mean} (equation (11)). The elastance coefficient (k) determines how quickly the ICP will rise as a result of an added volume of CSF at any given ICP, but the relation between volume and ICP changes, i.e. the compliance of the CSF system, is also dependent on the ICP level. The higher the ICP is when additional volume is added, the more the ICP level will increase. Along with k , the parameter (ICP_r-P_o) determines the compliance at baseline, and thus the initial rate at which ICP rises (and the initial value of AMP). The actual volume increase of the CSF system is not only dependent on the infusion rate, but also on the rate of absorption which will increase as ICP increases. How quickly CSF is absorbed at a certain ICP is determined by R_{out} , and during constant infusion an ICP level will eventually be reached where the absorption balances the external infusion and ICP stabilizes at a plateau pressure. Thus, R_{out} determines at which level ICP will cease to increase. Secondly, k and ΔV influence AMP_{mean} directly through the composite parameter RPPC (equation (13)), which determines how the amplitudes increase with ICP.

The analysis of parameter influence revealed how sensitive AMP_{mean} was to changes in the different CSF dynamic parameters corresponding to an expected range of values for patients investigated for NPH. The results (figure 4) showed that the elastance coefficient k had the strongest influence on AMP_{mean} in the expected range, followed by (ICP_r-P_o). These parameters both relate to compliance – ICP_r-P_o to baseline compliance and k to compliance at all ICP levels, and thus the increase of ICP and AMP throughout the infusion. R_{out} , which determines the final plateau pressure of the infusion, showed the least influence on AMP_{mean} . This suggests that the speed with which ICP was increased had a larger influence on AMP_{mean} than the level at which ICP stabilized, at least for the relatively short period of 10 minutes, and that compliance may be the key to the prognostic power of AMP_{mean} for selecting NPH patients for shunt surgery which was previously demonstrated by Eide and Brean.[16]

Though k had the smallest correlation coefficient of the parameters it is important to note that when correcting for RPPC in the partial correlation analysis the influence of k through this parameter is compensated for, and thus only the influence of k relating to changes in ICP_{mean} was analyzed. RPPC, which had the largest correlation coefficient, thus includes the direct correlation of both k and ΔV to AMP_{mean} . In the

parameter influence analysis, where k showed the strongest influence, the effect of changes in RPPC due to changes in k was included in the analysis of the influence of k . ΔV was not included in the parameter influence analysis as the appropriate range of variation for ΔV would have to be indirectly calculated from estimated values of the parameters k and RPPC, and would be unreliable due to propagation of uncertainties from these parameters. ΔV has not been extensively investigated in NPH, though it can be measured using phase contrast MR imaging. There are however inconsistencies between methods of estimation of ΔV used by different research groups, which further complicates the issue of determining an expected range of values. It is clear that ΔV will affect AMP_{mean} , but the prognostic relevance of this effect is difficult to determine without an estimate of an expected range of variation. The degree to which ΔV varies in NPH patients, and how this variation effects ICP pulse pressure, should be investigated in a study incorporating both MR and infusion investigations.

The authors who originally suggested AMP_{mean} as a prognostic test for NPH derived the test parameter empirically[16]. Previously they have shown impressive prognostic results for the AMP level during intracranially measured overnight ICP data[17], and they attempted to reproduce the results using data from lumbar infusion investigations. AMP determined at baseline (AMP_r) did not produce the same prognostic accuracy, but AMP_{mean} approached the results achieved with overnight monitoring. Our results support the emphasis on compliance suggested by the original study. The overnight monitoring contains information about the reaction of the system to internal perturbations which will lead to more or less variation in AMP depending on the compliance of the CSF system. Corresponding information is collected during an infusion test when the CSF system is exposed to an external perturbation, which will lead to larger or smaller AMP increase depending on the compliance. Important knowledge gained from this study was that, if further clinical studies confirms the effectiveness of AMP_{mean} to select NPH patients for shunt surgery, it supports the recent focus on the compliance and pulsatility aspect of CSF dynamics, rather than R_{out} , in research into the pathophysiology of NPH[9, 19, 23, 27].

The modelled values of AMP_{mean} were well matched to the clinically measured values (figure 3), which supports the effectiveness of the CSF dynamic model. The two patients mentioned in the methods section, where the CSF dynamic model was not completely applicable, correspond to two of the three cases with the largest discrepancy between the modelled and measured AMP_{mean} (figure 3). We have previously shown that AMP will reach a minimum level at an ICP close to P_o and remain here, or even increase slightly, if ICP is reduced further[31]. This corresponds to compliance reaching a maximum level, below which it remains essentially constant. For these patients the theoretical estimate of baseline compliance was not correct since the model was not valid for the initial stages of the investigations.

Patients with ICP_r below the model range may be wrongly classified in some prognostic tests based on constant infusion data (e.g. R_{out}) due to less accurately

estimated CSF dynamic parameters. The prognostic test investigated in this study, however, may in fact specifically identify these patients as unlikely to respond to shunt surgery as the AMP level will not rise during infusion until the ICP has increased enough to enter the phase where the model is applicable. AMP_{mean} is therefore likely to be low in these patients. The theory that these patients are less likely to respond to shunt surgery is in agreement with our previous findings[32], and it is potentially explained by these patients suffering from large ventricles due to brain atrophy rather than NPH[12].

The clinical value of this study was in the physiological interpretation of a parameter which has previously been shown to be effective when selecting NPH patients for shunt surgery. While the expression derived in this study is valid only for constant rate infusion, the results of the parameter influence analysis could be used to design new prognostic tests. The large observed affect on the test parameter AMP_{mean} from variations in compliance suggests that most of the prognostic information may stem from compliance. However, in patients with very high R_{out} AMP_{mean} may be high even if compliance is relatively normal, and thus it may be a mistake to disregard R_{out} entirely from NPH prognostics. Suspected NPH populations are often heterogeneous, which may suggest that the best prognostic tests are those which, like AMP_{mean} , combine the effects of several parameters which may be critically altered in the disease.

Conclusions

In this study the contributing CSF dynamics of a prognostic test for NPH based on mean intracranial pulse pressure amplitudes during a constant infusion test were analysed. The results showed that the parameters relating to the compliance of the CSF system had the strongest influence on the amplitude. This emphasizes the importance of analysing compliance aspects in infusion tests, and supports the theories that propose that compliance, and thereby also pulsatility, are the crucially affected aspects of CSF dynamics in NPH.

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Appendix

The volume change of CSF over time can be written as:

$$\frac{dV}{dt} = I_f - I_a + I_{ext}. \quad (15)$$

I_f and I_a are equal at ICP_r and thus, with the assumption than formation is pressure independent[4], I_f can be described using equation (4):

$$I_f = \frac{(ICP_r - P_d)}{R_{out}}. \quad (16)$$

Equation (15) can then be rewritten as:

$$\frac{dV}{dt} = \frac{(ICP_r - P_d)}{R_{out}} - \frac{(ICP - P_d)}{R_{out}} + I_{ext} = \frac{(ICP_r - ICP)}{R_{out}} + I_{ext}. \quad (17)$$

The derivative of ICP with respect to time (equation (3)) can thus be expressed as:

$$\frac{dICP}{dt} = \frac{k(ICP - P_0)}{R_{out}} (ICP_r - ICP + R_{out}I_{ext}). \quad (18)$$

The variable substitution $x = 1/(ICP - P_0)$, or $ICP = 1/x + P_0$, gives:

$$\frac{dICP}{dt} = \frac{dICP}{dx} \frac{dx}{dt} = \frac{-1}{x^2} \frac{dx}{dt}. \quad (19)$$

In equation (18) this results in:

$$\frac{-1}{x^2} \frac{dx}{dt} = \frac{k}{xR_{out}} \left(ICP_r - \left(\frac{1}{x} + P_0 \right) + R_{out}I_{ext} \right). \quad (20)$$

Rearranging this equation gives:

$$\frac{dx}{dt} + \frac{kx}{R_{out}} (ICP_r - P_0 + R_{out}I_{ext}) = \frac{k}{R_{out}}. \quad (21)$$

Equation (21) can be solved using the integrating factor (IF) method, where

$$IF \frac{dx}{dt} + IF \frac{kx}{R_{out}} (ICP_r - P_0 + R_{out}I_{ext}) = IF \frac{k}{R_{out}} \quad (22)$$

with the appropriate IF results in:

$$\frac{d}{dt} (IFx) = IF \frac{k}{R_{out}} \quad (23)$$

and thus:

$$x = \frac{\int IF \frac{k}{R_{out}} dt + A}{IF} \quad (24)$$

where A is a constant.

In this case the appropriate IF is:

$$IF = \exp\left(\int \frac{k(ICP_r - P_0 + R_{out}I_{ext})}{R_{out}} dt\right) = e^{tk(I_{ext} + (ICP_r - P_0)/R_{out})}. \quad (25)$$

For constant infusion ($I_{ext} = \text{constant}$) starting at ICP_{start} ($ICP(0) = ICP_{start}$), the following equation for ICP as a function of time is then derived:

$$ICP(t) = \frac{(R_{out}I_{ext} + ICP_r - P_0)(ICP_{start} - P_0)}{ICP_{start} - P_0 + (R_{out}I_{ext} + ICP_r - ICP_{start})e^{-tk(I_{ext} + (ICP_r - P_0)/R_{out})}} + P_0. \quad (26)$$