

Can NPH be caused by cerebral small vessel disease?

A new look based on a mathematical model

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1 Introduction

THE CLINICAL features of normal pressure hydrocephalus (NPH) are well known (FISHER, 1977). The mechanism by which cerebral ventricles enlarge in adult patients without overt increase in intracranial pressure is still speculative (SYMON and HINZPETER, 1976; OJEMAN and BLACK, 1982). Various tests have been suggested to obtain a satisfactory prediction with regard to which patient would benefit from a shunt procedure, but so far no one test has been recognised as being definitive.

In this communication we will report on a patient with NPH whose clinical course could be explained by application of a mathematical model of inter-relationships between brain compartments (SOREK *et al.*, 1988). This model may shed light on the still obscure aetiology of NPH.

2 Case report

A.K. is a 65-year-old merchant who started exhibiting signs of memory loss and impaired judgement. His appearance continued to be immaculate and small talk did not reveal his deficit. CT scans demonstrated an enlarged ventricular system. The fourth ventricle seemed less involved than the others and the CSF pressure on lumbar puncture was 120 mm H₂O. RHISA cisternography showed rapid entrance of the isotope into the ventricles; it cleared only after more than 48 h.

A shunting procedure was suggested but the family elected to wait. The patient's condition slowly deteriorated, his dementia became overt and he was confined to home. Six months later another consultation was sought because of progressive ataxia. Repeat CT scans revealed further enlargement of the hydrocephalus. Only 4 months later, when the patient was confined to bed due to severe ataxia, incontinence and speechlessness did the guardian permit

operation. CSF pressure at that time was 115 mm H₂O.

A ventriculo/peritoneal shunt with an opening pressure of 90 mm H₂O was installed. The postoperative course was remarkable for the rapid return of speech, memory, ambulation and continence. A month after the operation the patient returned to his business and several weeks later reported success in complicated financial considerations and decisions. CT scans demonstrated small, well drained ventricles.

Eight months later the patient started to deteriorate and within 3 weeks he was approaching his preoperative condition. CT scans again revealed enlarged ventricles (Fig. 1).



Fig. 1 Enlarged lateral ventricles in spite of a patent medium-pressure ventriculo/peritoneal shunt

Shunt malfunction was presumed but surgical revision failed to demonstrate any obstruction and did not alter his condition. Only after installment of a new shunt system with a low opening pressure (60 mm H₂O) did the patient improve. Once again, the patient's recuperation was remarkable; he is back at work and doing well. The CT

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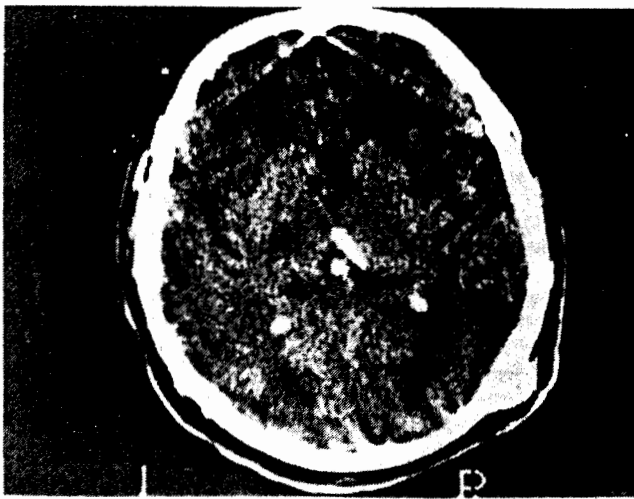


Fig. 2 Well drained ventricles after installment of a low-pressure ventriculo/peritoneal shunt

scan (Fig. 2) is evidence of a well drained ventricular system.

3 Discussion

In recent papers (KARNI *et al.*, 1987; SOREK *et al.*, 1988) a model depicting the brain as an assembly of interacting compartments has been put forward. The model (Fig. 3) solves the distribution of pressures, fluxes, resistances and compliances within these compartments.

In this model we attempt to define each intracranial structure as a cell. Seven such cells—arteries (A), capillaries

and choroid plexus (C), veins (V), venous sinuses (S), ventricular cerebrospinal fluid (F), jugular bulb (J) and brain tissue (B)—are lumped together and their interactions are described by a series of flux balance equations (SOREK *et al.*, 1988).

As an example, let us consider the equation describing flux balance for the capillary compartment.

$$\frac{P_A - P_C}{R_{AC}} = \frac{P_C - P_F}{R_{CF}} + \frac{P_C - P_B}{R_{CB}} + \frac{P_C - P_V}{R_{CV}} + C_{CF} \frac{d}{dt} (P_C - P_F) \quad (1)$$

where

P_A	= arterial pressure
P_C	= capillary pressure
P_F	= CSF pressure (ventricular)
P_B	= brain tissue pressure
P_V	= venous pressure
R_{AC}	= resistance to flow between arteries and capillaries
R_{CF}	= resistance of flow between capillaries and ventricular CSF
R_{CB}	= resistance to flow between capillaries and brain tissue
R_{CV}	= resistance to flow between capillaries and vein
C_{CF}	= compliance factor between choroid plexus and ventricular CSF
$(d/dt)(P_C - P_F)$	= time derivative of the pressure difference between choroid plexus and ventricular CSF

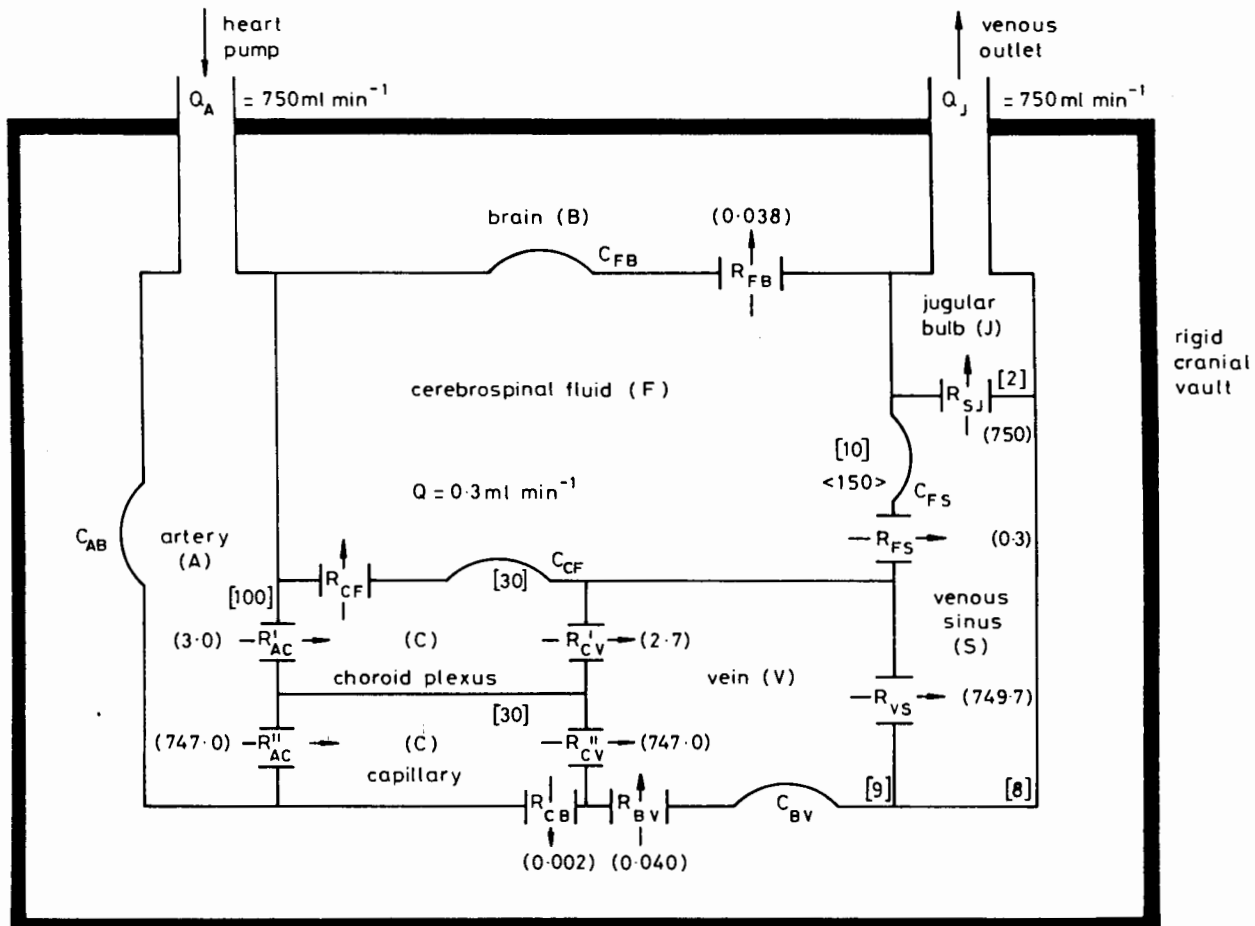


Fig. 3 Lumped-parameter seven-compartment model of the intracranial cerebrovascular fluid systems

R: resistance () flow, ml min^{-1}
 C: compliance < > volume, ml
 []: pressure, mm Hg

As a first approximation the resistances and compliances were considered as mean effective values, i.e. constants. The overall matrix of resistances and compliances were evaluated via an inverse procedure (SOREK *et al.*, 1988).

Note that eqn. 1 describes the flux balance in quasi-steady as well as in nonsteady situations. The cells may be rigid, giving a flux term expressed by time-dependent pressure differences divided by resistance, or contractile, yielding a flux which is the product of compliance and time changes of pressure differences.

In the course of evaluating the resistances of the model it was shown that a situation leading to evolution of a 'normotensive' hydrocephalus may take place. The usual accepted mechanism for development of hydrocephalus is defective absorption of CSF in the venous sinus. In our mathematical model this will be expressed by $R_{FS} = \infty$ or $Z_{FS} = 1/R_{FS} = 0$ (where R_{FS} is the resistance to flow between the ventricular CSF compartment and venous sinus compartment and where Z_{FS} stands for the conductance between these compartments). However, it was shown (SOREK *et al.*, 1988) that at the same time the resistance R_{CB} between capillaries (C) and brain tissue (B) may attain infinite values $R_{CB} = \infty$.

In the set of equations for the solution of the model resistances we have relationships between fluxes, pressure differences and coefficients α and β .

$$\alpha = \frac{R_{FB}}{R_{VS}} \quad (2)$$

$$\beta = \frac{R_{FB}}{R_{CB}} \quad (3)$$

The scalar coefficients α and β account for the double redundancy due to four independent flux-balance equations and six unknown conductances. From the physiological aspect, α indicates the ratio of the cerebrospinal fluid/brain barrier to the vein/venous sinus resistance, whereas β is the ratio of the cerebrospinal fluid/brain barrier to the blood/brain barrier. The actual values of α and β are determined by a sensitivity analysis, requiring that the conductances and compliances be sufficiently insensitive to changes in these values. The values of $\alpha = 10^4$ and $\beta = 10^{-3}$ were found to satisfy this condition. With known values of α and β we now have a set of equations that can be solved for all the unknown conductances (eqn. 21, SOREK *et al.*, 1988).

For instance, the relationship between Z_{CB} (conductance between capillaries and brain tissue) and Z_{FS} (conductance between ventricular CSF and venous sinus) is as follows:

$$Z_{CB} = \frac{\beta(Q_A^* - Q_F^*)}{\alpha(P_V^* - P_S^*) - (P_V^* - P_B^*)} \quad (4)$$

$$Z_{FS} = \frac{\alpha(P_V^* - P_S^*)Q_F^* - (P_F^* - P_B^*)Q_A^*}{(P_F^* - P_S^*)[\alpha(P_V^* - P_S^*) - (P_F^* - P_B^*)]} \quad (5)$$

where (*) denotes mean effective values

Q_A = flux entering the arterial compartment

Q_F = flux entering the CSF compartment = CSF generation

Q_F may be described by

$$Q_F = \frac{P_C - P_F}{R_{CF}} \quad (6)$$

One should not interpret the use of the constant (average) conductances values as implying steady state. They are obtained by taking time averages in a nonsteady process. Once all compliances and conductances have been

determined, it is possible to solve for the nonsteady pressures and fluxes in the cerebrovascular system.

It is noteworthy to investigate the solution for the conductances in abnormal cases indicated by extreme values of β and α . A solution of the set can be attained when we allow $\beta = 0$. In this case we are left with three possibilities for choosing the α value:

- $\alpha = 0$ This choice yields some negative conductances which are unacceptable.
- $\alpha = (P_F^* - P_B^*)/(P_V^* - P_S^*)$ all conductances indicate a destruction of all flow passages.

We therefore rule out those two choices.

An accompanying condition $Z_{FS} = 0$ will still yield a possible solution.

Thus the following mathematical equations now exist:

$$Z_{CB} = 0 \quad (R_{CB} = \infty) \quad (7)$$

$$Z_{FS} = 0 \quad (R_{FS} = \infty) \quad (8)$$

$$\alpha Q_F^*(P_V^* - P_S^*) - Q_A^*(P_V^* - P_B^*) = 0 \quad (9)$$

Eqn. 7 is the mathematical representation of a flow impediment between the capillaries and the brain tissue. The condition $Z_{CB} = 0$ may be regarded as a precondition activating the NPH situation represented by eqns. 8 and 9.

Conditions expressed by eqns. 8 and 9 indicate blockage of CSF transfer from the ventricles to the venous sinus. As these conditions do not affect production of CSF by the choroid plexus ($Q_F = 0$) compartment, (F) will expand. The presence of compliances C_{FB} , C_{FS} and C_{CF} (Fig. 3) allow for the expansion without increase of pressure, i.e. NPH.

Thus, in a situation where the flow from capillaries to brain tissue is impaired, as may be the case in arteriosclerotic cerebrovascular disease and especially in small vessel disease in the aged, an NPH may develop.

To overcome the NPH situation one has to interfere with the balance as stated in eqn. 9. By lowering the CSF pressure P_F , i.e. shunting procedure, the previous conductivities may change in a step fashion accommodating the new mean pressures and fluxes as indicated by eqns. 4 and 5. Note that according to eqn. 9 such step changes may also take place when changing other factors, e.g. P_V , P_S . Thus removal of CSF will also yield a change in capillary to brain tissue transfer, which may explain the improvement in neurological functions after shunting. It was shown that CSF drainage in hydrocephalic patients increases regional cerebral blood flow (SYMOM and HINZPETER, 1976). If the small vessel disease continues, eqn. 9 may again prevail and a further decrease in CSF pressure is necessary to accommodate the new resistances and compliances. This could be the case in our patients.

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Communication

Dielectric properties of fluid-saturated bone: a comparison between diaphysis and epiphysis

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1 Introduction

THERE HAS RECENTLY been great interest in the study of the dielectric properties of bone due to the growing importance of electrical stimulation of osteogenesis in orthopaedic therapy. Several investigators have measured the dielectric properties of fluid-saturated bone as a function of frequency (ERIKSSON, 1976; CHAKKALAKAL *et al.*, 1980; KOSTERICH *et al.*, 1983; 1984; SINGH and SAHA, 1984; REDDY and SAHA, 1984; SAHA *et al.*, 1984). Up to now the measurements have been performed *in vitro* on mid-diaphyseal samples generally obtained from bovine or rat femurs. The results of these studies allow electrical modelling of bone and the correlation of bone permittivity and conductivity with its microstructure. The object of this study is to determine the dielectric characteristics in the proximal and distal epiphyses of femur and to compare them with those of the diaphyses.

2 Experimental method

2.1 Specimen preparation

A bovine femur was used to extract the samples to be measured. One sample was cut at each of the four positions indicated in Fig. 1. The samples in the three cuts of the epiphyses (CC, CC₁ and D) have thicknesses of 2–4

2.8 mm, areas of 61 mm² and were oriented so that their large surfaces were normal to the axial direction. Their locations are shown in Fig. 2. The sample from the diaphysis (F₂) had a thickness of 1.3 mm, an area of 29 mm² and was also orientated so that its large surfaces were normal to the axial direction, as shown in Fig. 3. The final dimensions were obtained by wet milling at low speed to avoid surface damage. After milling, and to remove the debris produced by machining without significantly affecting the bone marrow, the samples were briefly cleaned for 2 min in an ultrasonic bath in deionised water at room temperature. Once cleaned, the samples were immersed and kept in physiological solution until used for measurement.

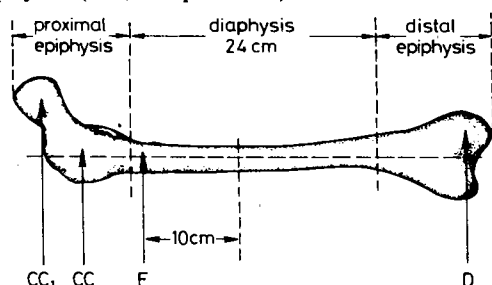


Fig. 1 Positions of the samples cut from the diaphysis and the proximal and distal epiphyses of a bovine femur. The mid-diaphyseal plane is shown for reference

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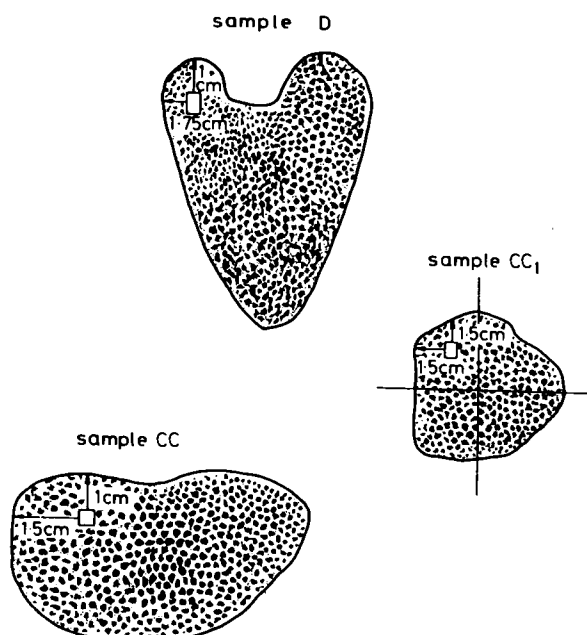


Fig. 2 Location of the samples in the three cuts of the epiphyses. CC and CC₁ were from the proximal epiphysis and D was from the distal epiphysis. The planes shown are normal to the axial direction