

6 INTRACRANIAL PRESSURE AND ELASTANCE

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6.1 The problem: raised intracranial pressure after head injury

6.1.1 INTRODUCTION

Head injury is a common form of trauma. For example, in the UK head injury occurs in more than 500 000 persons per annum of which about 10% are diagnosed as severe, 15% moderate and the remainder as minor head injury (Miller et al., 1992; Pickard and Czosnyka, 1993). Head trauma is a significant cause of death and disability, especially in young males (median age < 30) and is associated with raised intracranial pressure (ICP). Raised ICP is defined as pressure greater than 20 mmHg and appears most commonly in about 50–75% of patients with severe head injury who remain comatose after resuscitation.

Over the past 50 years there has been an active and wide-ranging research into the causes and consequences of raised ICP which, to date, has been the subject of nine international symposia embracing such diverse disciplines as neurosurgery, anaesthesia, radiology, biophysics, electronic and mechanical engineering, mathematics and computer science.

In particular, the introduction during the 1970s of the continuous monitoring of ICP has led to renewed activity in both clinical and experimental research into the physiology and pathophysiology of maintaining craniospinal volume and pressure. *This interest has not just been in monitoring pressure alone but also in using information derived from pressure monitoring to help both predict raised ICP and determine the underlying cause.*

ICP is a reflection of the relationship between alterations in craniospinal volume and the ability of the craniospinal axis to accommodate added volume. The craniospinal axis is essentially a partially closed box with container properties including both viscous and elastic elements. The elastic or its inverse, the compliant, properties of the container will determine what added volume can be absorbed before intra-

cranial pressure begins to rise. So an understanding of raised ICP encompasses an analysis of both intracranial volume and craniospinal compliance.

This chapter reviews the relationship of raised ICP to outcome and its significance as part of the development of the primary injury and as a superimposed secondary insult. This is followed by a review of both the historical and current concepts underlying our present understanding of the physiology and pathophysiology of maintaining intracranial pressure and volume.

6.1.2 RAISED INTRACRANIAL PRESSURE: RELATIONSHIP TO OUTCOME

Raised ICP has in the past been found to be associated with a poorer outcome from injury with the higher the level of ICP, particularly the peak ICP level, correlating with the expected prognosis for mortality and morbidity (Becker et al., 1977; Marshall et al., 1979; Miller et al., 1977, 1981; Pitts et al., 1980). There has, however, been controversy over the usefulness of monitoring raised ICP with some groups, with a 'no ICP monitoring' policy, finding in their studies of head injury mortality and morbidity that outcome is similar to other groups that do monitor ICP (Stuart et al., 1983). Reported differences in the utility of ICP monitoring could be due to variability in both management and monitoring protocols between different neurosurgical centers. Variation in type of ICP pressure monitor, site of placement, treatment thresholds, patient referral characteristics and outcome measures can all combine to produce a large variability in both measured ICP and outcome, irrespective of whether ICP is monitored or how it is treated. Another source of variation in terms of raised ICP is the inherent variability of the head-injured population, outcome being dependent on a number of other factors. For example, mass lesions are generally accompanied by elevations in ICP of greater than 40 mmHg and are associated with poorer outcome, while diffuse injuries

tend to have lower ICP levels associated with a similarly poor outcome (Miller *et al.*, 1977, 1981). Age is also an important factor, with an age-dependent distribution of ICP for both type of injury and outcome. This is particularly so for pediatric cases (Alberico *et al.*, 1987; Choi *et al.*, 1991; Luerssen, Klauber and Marshall, 1988; Volmer *et al.*, 1991). ICP can even be raised in the absence of overt signs of swelling or mass lesions on CT. *In a small study of severely head-injured patients, O'Sullivan et al. (1994) demonstrated that some comatose head-injured patients whose initial CT scan was normal, with no mass lesion, midline shift or abnormal basal cisterns, developed raised ICP greater than 20 mmHg that lasted longer than 5 minutes. This included a subset of patients showing pronounced raised ICP of greater than 30 mmHg.*

Data from large prospective trials carried out from single centers and from well-controlled multicenter studies have provided the most convincing evidence for a direct relationship between ICP and outcome (Narayan *et al.*, 1981; Saul and Ducker, 1982; Marmarou *et al.*, 1991; Jones *et al.*, 1994). Narayan *et al.* (1981), in a prospective study in 133 severely head-injured patients, demonstrated that the outcome prediction rate was increased when the standard clinical data, such as age, Glasgow Coma Score on admission (GCS) and pupillary response with extraocular and motor activity, was combined with ICP monitoring data. Marmarou *et al.* (1991), reporting on 428 patients' data from the National Institute of Health's Traumatic Coma Data Bank, showed that, following the usual clinical signs of age, admission motor score and abnormal pupils, the proportion of hourly ICP recordings greater than 20 mmHg was the next most significant predictor of outcome. Outcome was classified by the Glasgow Outcome Score (GOS) at 6 months follow-up. They also found, using stepwise logistic regression, that, following ICP, arterial pressure below 80 mmHg was also a significant predictor of outcome. Jones *et al.* (1994) studied prospectively 124 adult head-injured patients during intensive care using a computerized data collection system capable of minute-by-minute monitoring of up to 14 clinically indicated physiological variables. They found that ICP above 30 mmHg, arterial pressure below 90 mmHg and cerebral perfusion pressure below 50 mmHg significantly affected patient morbidity.

Although in the past there have been differing opinions about the contribution of continuous monitoring of ICP to reduction in mortality and morbidity following head injury, there is now sufficient evidence to remove doubt about the value of ICP monitoring towards improving the prediction of outcome and allowing more informed decisions to be made about patient management.

6.1.3 RAISED INTRACRANIAL PRESSURE: RELATIONSHIP TO PRIMARY AND SECONDARY INJURY

Both experimental and clinical studies have clearly shown that, following traumatic brain injury, normal physiological mechanisms for maintaining cerebral perfusion can become impaired (Lewelt, Jenkins and Miller, 1980, 1982; Povlishock and Kontos, 1985; Nordstrom *et al.*, 1988; Miller and Adams, 1992). These studies demonstrate that brain injury can cause impairment or loss of autoregulation – defined as the ability of the cerebral vessels to respond to changes in arterial gases or to arterial pressure. As a result of these changes there can, at times, be a decrease in cerebrovascular resistance, which can lead to raised ICP in both adults and children (DeSalles, Muizelaar and Young, 1987; Jaggi *et al.*, 1990; Muizelaar *et al.*, 1989a, b; Uzzell *et al.*, 1986). While brain injured patients are being managed in intensive care there are, superimposed on the primary injury, periods of reduced P_{aO_2} or episodes of arterial hypotension often as a result of other injuries or treatment by hypnotic drugs (Rose, Valtonen and Jennett, 1977; Gentleman and Jennett, 1981; Miller *et al.*, 1981; Miller and Becker, 1982; Marmarou *et al.*, 1991; Jones *et al.*, 1994). With an impaired physiological mechanism unable to respond adequately to these adverse changes in physiological parameters (or 'secondary insults'), ischemic brain damage can occur. These secondary, chiefly ischemic brain insults are common with Graham, Hume Adams and Doyle (1978) reporting, in a series of 151 fatal cases of severe head injury, a 91% incidence of ischemic brain damage found on autopsy. A second study carried out by the same group over 10 years later found a similar high incidence (>80%) of ischemic brain damage despite subsequent improvements in intensive care of head-injured patients (Graham *et al.*, 1989). Other studies have shown that patients whose primary injury was judged not to have been severe (patients who 'talk and die') go on subsequently to deteriorate as a result of secondary largely avoidable events (Reilly *et al.*, 1975; Rose, Valtonen and Jennett, 1977; Sharples *et al.*, 1990). These studies were responsible for the concept of avoidable brain injury and stimulated considerable clinical and experimental research into both the pathophysiology of secondary brain damage and methods aimed at detecting and predicting adverse physiological conditions.

Grossman *et al.* (1975), studying the relationship between cortical electrical activity and cerebral blood flow (CBF) and CPP during CSF infusion in non-head-injured primates, showed the relevance of maintaining adequate cerebral perfusion. Provided CBF

and CPP were preserved, electrical activity was maintained despite ICP increases above 50 mmHg. However, the cortical activity rapidly disappeared when CBF fell markedly, to levels below approximately 20 ml/100 g/min. Narayan *et al.* (1981) confirmed the importance of brain electrical activity as a marker for adequate cerebral perfusion in head-injured patients. In a prospective study of 133 patients he demonstrated that multimodality evoked potentials when taken together with both basic clinical signs and ICP formed the best predictive model of outcome. More recent studies of brain electrical activity have again reaffirmed the association between outcome, ICP and brain electrical activity. Park *et al.* (1993) studied a small group of patients classified as having minor, moderate or severe diffuse axonal injury (DAI) with serial monitoring of multimodality evoked potentials over 4 weeks. Patients were followed up at 3 months and assessed using the Glasgow Outcome Score. Patients with both moderate and severe DAI showed marked changes in somatosensory and visual evoked potentials, which were correlated with outcome. Increasingly, motor evoked potentials elicited by transcranial electrical or magnetic stimulation are also being studied as potential measures of neurological function in neurotrauma patients. Kawai *et al.* (1993), in a feline model of diffuse brain compression, monitored the central motor pathways by transcranial magnetic stimulation of the motor cortex. They found that the N4 component (4.99 ms latency) of the spinal motor evoked

potential (L1–L2) was progressively prolonged and depressed as ICP rose above 40 mmHg.

Apart from cerebral electrical measurements as an indication of neurological function, there has been much interest in the relationship between ICP, CPP and CBF. The landmark study of Miller, Stanek and Langfitt (1972) produced some of the first experimental evidence confirming the concept that changes in intracranial pressure affect cerebral blood flow not directly but through changes in cerebral perfusion pressure (CPP), where CPP is defined as the difference between mean arterial pressure and intracranial pressure. Strictly speaking, the actual cerebral perfusion outflow pressure would be cerebral venous pressure, although it is, in most situations, impractical to measure this pressure routinely. However it has been established that over a wide range of pressures cerebral venous pressure is well approximated (within 3–4 mmHg) by ICP (Johnson and Rowan, 1974; Yada, Nakagawa and Tsuru, 1973; Nakagawa, Tsuru and Yada, 1974). In an experimental study of CBF as determined by the venous outflow technique in dogs, Miller also demonstrated that, when MAP and ICP rise in parallel so that CPP remains constant at 60 mmHg, CBF increases with MAP in animals found to be non-autoregulating. It was further shown that, as CPP drops in autoregulating animals, the breakpoint at which CBF starts to decrease is at a higher level if CPP is reduced through hemorrhagic arterial hypotension than if it is reduced through intracranial hypertension (Figure 6.1). This work suggests that cerebral

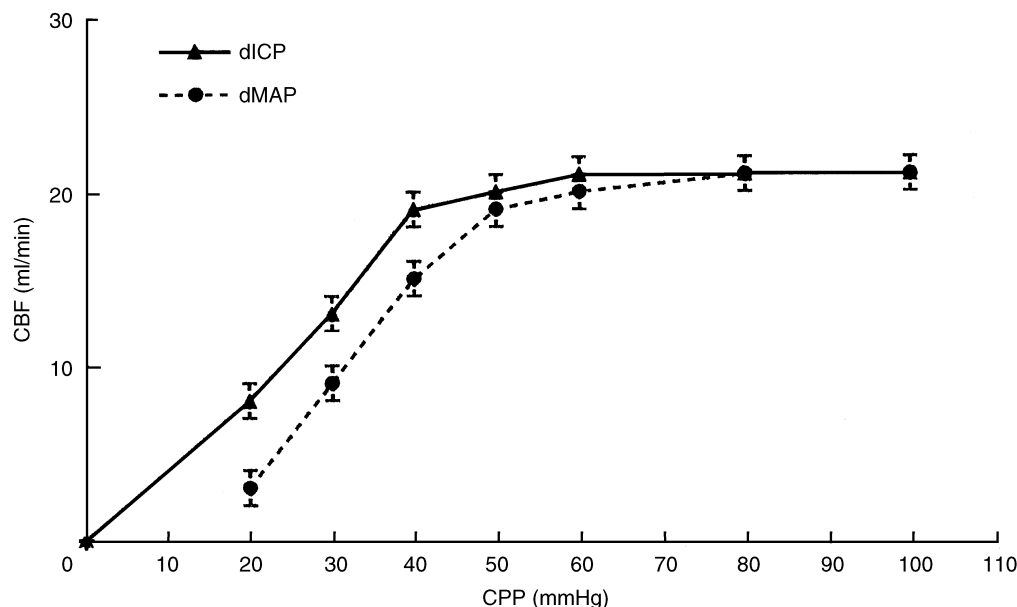


Figure 6.1 Plot showing that the breakpoint at which cerebral blood flow (CBF) starts to decrease is at a higher level if cerebral perfusion pressure (CPP) is reduced through hemorrhagic arterial hypotension (dMAP) than if it is reduced through intracranial hypertension (dICP).

perfusion is more sensitive to arterial hypotension than to intracranial hypertension.

The clinical significance of this information is that in the management of head injury it is often necessary to employ therapy to lower raised ICP. Therapeutic agents for reducing raised ICP often do so at the expense of reduced MAP and as a consequence CPP may not improve. If autoregulation is preserved, CBF should remain unchanged despite parallel changes in MAP and ICP. However, clinically, autoregulation is likely to be impaired in those conditions in which ICP is increased such as head injury or subarachnoid hemorrhage (Harper, 1966; Muizelaar, Lutz and Becker, 1984; Muizelaar and Becker, 1986; Muizelaar *et al.*, 1989a, b; Obrist *et al.*, 1984; Bouma and Muizelaar, 1990). Under these circumstances, it is important that reduction in ICP should not be achieved at the expense of lowering CBF and provoking brain ischemia.

This earlier work of Miller was later extended by Chan, Miller and Piper (1992) to include CPP ranges of 60, 50 and 40 mmHg. At CPP levels of 50 and 60 mmHg, when autoregulation was intact, CBF remained unchanged. However, with loss of autoregulation, there was a trend for CBF to increase as MAP and ICP were increased in parallel at a CPP of 50 and 60 mmHg. Absolute CBF levels were significantly different between the autoregulating and non-autoregulating groups. At a CPP of 40 mmHg CBF showed a linear correlation with BP. This work demonstrates that, when autoregulation is impaired, there is a functional difference between autoregulating and non-autoregulating cerebral vessels despite similar MAP and CPP and that, when autoregulation is impaired, CBF depends more on arterial driving pressure than on cerebral perfusion pressure.

The importance of arterial pressure as the prime factor governing CPP-related secondary insults has been well demonstrated by the recent work by Jones, Miller and colleagues (1994) who carried out a prospective study over 4 years of the frequency and severity with which secondary insults occur to head-injured patients while being managed in intensive care. They developed a microcomputer-based data collection system that allows the acquisition of data from up to 15 monitored variables minute by minute (Piper *et al.*, 1991). At each bedside data collection was under the control of a microcomputer; serial links between the patient monitors and the microcomputer allow the controlled transfer of multiple channels of physiological data once per minute. The controlling software allowed medical staff to add comments to the current active computer file at any time, precisely annotating significant events. The software performs artifact detection, calculates derived data and highlights valid data that falls

outside normal physiological levels. Collected data was stored to disk and can be printed either locally or remotely.

From the valid physiological data produced, manual processing of data was used to identify secondary insults, which are defined at one of three grades of severity and which must last for 5 minutes or longer to be recorded as an insult. This permits calculation of the frequency, severity and total duration of insults, measured in minutes.

An analysis was made of 124 adult head-injured patients who were monitored during intensive care using the computerized data collection system. Information was logged at 1 minute intervals and scanned to identify insults when values fell outside threshold limits for 5 minutes or longer. Three grades of insult were defined for each variable. The duration of insults has been analyzed in relation to the Glasgow Outcome Score of these patients at 12 months after injury. The monitored patients included 68 with severe head injury (Glasgow Coma Score of 8 or less with no eye-opening), 36 with moderate head injury (GCS 9–12) and 20 with minor head injury (GCS 13–15 but with multiple injuries, scoring 16 or more on the Injury Severity Scale).

Insults were found in 91% of patients at all degrees of severity of head injury. 10% of patients had insults that were only at the lowest Grade 1 level, 31% had insults at both Grade 1 and Grade 2 levels and 50% of patients had at least one insult at Grade 3 level in addition to Grade 1 and 2 insults. Overall, the majority (77%) of all insults detected in the ITU were at Grade 1 level and these represented 85% of the total duration in minutes of insult measured.

In a subset of 71 patients (51 severe, 18 moderate and two minor), all of whom had six channels monitored concurrently (ICP, BP, CPP, S_aO_2 , body temperature, heart rate) insult and outcome data were analyzed using stepwise logistic regression to determine the effects of age, admission GCS score, pupil responses, injury severity score and insult duration on outcome scored on the Glasgow Outcome Scale at 12 months. Duration of hypotension, hypoxemia and pyrexia were found to be significant predictors of mortality. When good *versus* bad outcome was considered (good recovery and moderate disability *versus* severe disability and death), the logistic regression analysis showed duration of hypotension and bilateral loss of pupil light response to be the most important predictors.

Differences in the duration of insult between outcome groups 12 months postinjury were compared with each grade of insult, using Kruskal–Wallis one-way analysis of variance and by Mann–Whitney U tests. Significant differences in the distribution of hypotensive insults was found between the outcome

grades at all levels of severity of insult. Similar results were found for cerebral perfusion pressure insult duration. These data confirm the important adverse effect of even moderate reductions in arterial pressure (systolic BP less than 90 mmHg or mean BP less than 70 mmHg).

Miller and coworkers further considered whether the estimate of the burden of secondary insults was excessive, as a result of selection of an atypical group of head-injured patients. This was not the case, as the mortality rates for severe, moderate and minor head injury were 31%, 11% and 5% respectively. The other possibility is that the computerized system is more efficient in the detection of abnormal values in monitored variables than the nursing staff in the intensive care unit. This was examined by an additional study (Corrie *et al.*, 1993), where the number, duration and severity of computer-identified insults were compared with the values recorded by nursing staff on the standard intensive care unit bedside 24-hour chart. Data from computer recordings and nursing charts from 20 head-injured patients were compared for 37 periods, each of a full 24 hours, during which data from four selected channels were obtainable without interruption. Insults detected using the computer system were divided into those completely identified, completely missed or partially identified on the bedside nursing chart. Of 216 periods of insult of 5 minutes or longer that were identified using the computer system, 69 (32%) were missed on the standard bedside nursing chart. The majority of these missed insults were at Grade 1. Insults at Grade 2 or Grade 3 level were more likely to be recorded on the nursing chart. However, of all the insult types studied, Grade 1 arterial hypotension was most often missed (94%). Charting accuracy improved to 87% detection of computer-identified insults when those insults that crossed the designated hour and half hour recording slots in the nursing chart were considered. Insults that lasted less than 30 minutes were significantly more likely to be missed than those that were longer. *While this study is reassuring in that the bedside nursing chart was reliable in the detection of most insults that involved raised ICP, it is a major concern that periods of mild arterial hypotension were frequently missed when outcome data indicates that even these relatively minor episodes have an adverse effect on patient outcome.*

Thus secondary insults are common, result in mainly ischemic brain damage and are a major contribution to disablement. They are important because they are common and yet so potentially avoidable. Clearly a critical challenge facing us is to develop patient monitoring systems and protocols that will lead to rapid detection and resolution of secondary insults.

6.2 The principles: physiology and pathophysiology of intracranial pressure

6.2.1 CONTROL OF INTRACRANIAL VOLUME AND PRESSURE: HISTORICAL CONCEPTS

The history of the subject of intracranial pressure has been well reviewed (Masserman, 1935a, Stern, 1963; Langfitt, 1969) and starts from *the doctrine named after Monro (1783) and Kellie (1824), which proposed that the brain and its contained blood were incompressible, enclosed in a rigid and inextensible skull, of which the total volume remained constant. In its original form the Monro–Kellie doctrine did not take into account the CSF as a component of the cranial compartment. The concept of reciprocal volume changes between blood and CSF was introduced in 1846 by Burrows and was later extended in the early 20th century by Weed and McKibben (1919; Weed, 1929) to allow for reciprocal changes in all the craniospinal constituents.*

Kocher in 1901 translated into clinical terms the four stages of cerebral compression proposed almost 25 years earlier by the experimental studies of Duret (1878). Kocher described four stages of cerebral compression related to the expansion of intracranial brain tumors. In stage 1, the initial increase in tumor volume is compensated by a reduction in volume of the other intracranial components, chiefly CSF and venous blood. This spatial compensation results in no net increase in intracranial volume or pressure and hence no clinical symptoms. In stage 2 the compensatory mechanisms are exhausted, ICP increases and the patient becomes drowsy, with headache. Stage 3 is characterized by a considerable increase in ICP, an associated deterioration in conscious level with intermittent elevations of blood pressure (BP) accompanied by bradycardia. In the fourth and final stage, the patient is unconscious, with bilateral fixed dilated pupils and falling BP, usually leading to death.

Cushing (1901, 1902, 1903), then a research worker for Kocher, described in both experimental and clinical studies the close relationship between increases in ICP and BP and proposed that the BP rose in order to maintain adequate blood supply to the hindbrain, the stimulus to this vasopressor response believed to be medullary ischemia (Jennett, 1961; Johnson and Rowan, 1974).

At about this time a false confidence developed in the lumbar CSF pressure technique (lumbar puncture) which caused Cushing's findings to be challenged. Reports emerged (Browder and Meyers, 1936; Smyth and Henderson, 1938; Evans *et al.*, 1951) that some patients showing clinical signs of brain compression had normal lumbar CSF pressures and that in other patients elevations in BP were found at times when ICP was well below the level of BP.

Partly because of this apparent dissociation between ICP and clinical symptoms, emphasis switched away from ICP measurement towards the relationship between craniospinal volume and pressure, particularly the importance of the elastic properties of the craniospinal system. Ayala (1923, 1925) studied the fall in lumbar pressure that occurred when CSF was removed from patients, describing the degree of decline in terms of the volume of CSF removed and the 'elasticity' of the meninges. 'Ayala's index' developed from this work and is defined as the fall in pressure divided by the volume of fluid removed. This index was found to be low in patients diagnosed with benign intracranial hypertension and high in patients with cerebral tumors.

Weed and Flexner (1932; Weed, Flexner and Clark, 1932; Flexner, Clark and Weed, 1932; Flexner and Weed, 1933) systematically studied the effect of hydrostatic columns on the elastic properties of the craniospinal system by observing the pressure and volume changes during up/down head-tilting experiments in animals. They defined a coefficient of elasticity based on Hook's law ($E_0 = \text{stress/strain}$), which failed to show any change under a variety of experimental conditions. Their work was critically reviewed by Massermann (1934, 1935a), who carried out similar studies in patients. *Ryder et al. (1951) were the first to characterize the craniospinal volume-pressure relationship as a non-linear quantity, describing it as a hyperbolic function, which implies an increase in elastance as pressure increases.* This was in conflict with the work by Weed and coworkers, although the latter group only studied the elastic properties over a limited physiological pressure range. Furthermore, it was also partly the work of Ryder *et al.* (1953) that restored confidence in intracranial pressure measurement by demonstrating a differential pressure between intraventricular and lumbar CSF pressure recording. This phenomenon was reported as early as 1895 by Bayliss, Hill and Gulland, who noted that it was impossible to obtain valid ICP measurements below the tentorium during later stages of progressive supratentorial brain compression.

It was not until the 1960s when Lundberg (1960) published his now classic monograph, that interest in clinical ICP measurement was rekindled. Using ventricular fluid pressure recording in brain tumor patients, Lundberg was the first to delineate the frequency with which raised ICP occurs clinically, at times reaching pressures as high as 100 mmHg. *Lundberg also described three types of spontaneous pressure wave fluctuations: 'A' waves or plateau waves of large amplitude (50–100 mmHg) with a variable duration (5–20 min), 'B' waves, which are smaller (up to 50 mmHg), sharper waves with a dominant frequency of 0.5–2/min, and finally 'C' waves, which are small*

(up to 20 mmHg), rhythmic oscillations with a frequency of 4–8/min.

This work was then extended to include head injuries (Lundberg, Troup and Lorin 1965; Johnston, Johnston and Jennett, 1970), intracranial hemorrhage (Richardson, Hide and Eversden, 1970), posthypoxic brain damage (Langfitt *et al.*, 1974) and benign intracranial hypertension (Johnston and Paterson, 1972). ICP can therefore increase under an assortment of experimental and clinical circumstances, the frequency often being underestimated by the lumbar pressure recording technique. This phenomenon of pressure underestimation was fully defined by Langfitt and coworkers (1964a, b) in experimental studies of extradural brain compression, where progressive loss of transmission of ICP across the tentorial hiatus occurred, with the pressure in the posterior fossa and lumbar subarachnoid space progressively under-reading the ventricular pressure and eventually returning to normal pressure.

Some of the most important work at this time was also carried out by Langfitt's group (Langfitt, Weinstein and Kassel, 1965) who redefined Kocher's four stages of cerebral compression under controlled experimental conditions in Rhesus monkeys with simultaneous measurement of arterial and intracranial pressure, jugular or sagittal sinus pressure, cerebral blood flow (CBF) and measures of brain metabolism. They defined stage 1 as the period of spatial compensation, with very little increase in ICP despite slow inflation of an extradural balloon. Electroencephalogram (EEG), CBF and brain oxygenation were normal and stable at this time. Stage 2 occurred at the end of spatial compensation and was characterized by an exponential increase in ICP with a steady extradural balloon inflation rate. Towards the end of this stage, ICP increased by more than 15 mmHg with 0.1 ml injections into the extradural balloon, and spontaneous increases in BP occurred that initiated further increases in ICP. Further waves of increased ICP could be triggered at this time by hypercapnia and hypoxia. In stage 3, ICP was approaching the level of BP, with the vasomotor reflexes becoming less effective in driving BP up above the ICP. EEG slowed and became flat as ICP reached the level of BP. At this stage, altering the arterial concentration of carbon dioxide ($P_a\text{CO}_2$) had no response, an effect which Langfitt termed 'vasomotor paralysis'. Also at this stage, induced changes in BP produced almost identical changes in ICP. Deflation of the balloon at this stage could cause a return of ICP to normal levels, with a partial return of EEG. If balloon inflation continued, stage 4 was entered, where decompensation was irreversible, BP dropped and death followed. Deflation of the balloon at this time resulted in only a temporary fall in ICP.

6.2.2 CONTROL OF INTRACRANIAL VOLUME AND PRESSURE: CURRENT CONCEPTS

Following on from this earlier work, the research carried out in the 1970s and early 1980s provides much of the basis for our current concepts of intracranial pressure and craniospinal compliance.

Marmarou, interested in CSF dynamics in relation to the pathological state of hydrocephalus, was the first to provide a full mathematical description of the craniospinal volume–pressure relationship. Marmarou (1973) developed a mathematical model of the CSF system that produced a general solution for the CSF pressure. The model parameters were subsequently verified experimentally in an animal model of hydrocephalus. As a corollary from this study, Marmarou demonstrated that *the non-linear craniospinal volume–pressure relationship could be described as a straight line segment relating the logarithm of pressure to volume, which implies a monoexponential relationship between volume and pressure (Figure 6.2). The slope of this relationship Marmarou termed the pressure–volume index (PVI) which is the notional volume required to raise ICP tenfold.* Unlike elastance (change in pressure per unit change in volume dP/dV) or its inverse, compliance (change in volume per unit change in pressure dV/dP), the PVI characterizes the craniospinal volume–pressure relationship over the whole physiological range of ICP.

The PVI is calculated from the pressure change resulting from a rapid injection or withdrawal of fluid

from the CSF space (Figure 6.3), and has found widespread use both clinically and experimentally as a measure of lumped craniospinal compliance (Marmarou, Shulman and LaMorgese, 1975; Sullivan *et al.*, 1977; Takagi *et al.*, 1980; Kosteljanetz, 1985; Shapiro *et al.*, 1985; Takizawa, Gabra-Sanders and Miller, 1986a; Maset *et al.*, 1987). Any factor increasing in volume within the craniospinal axis will deplete available compensatory exchange space (decompensation), reduce compliance and eventually lead to increased intracranial pressure. Shapiro and Marmarou (1982) have found a PVI reduced by 80% of control values to be predictive of raised ICP in pediatric head injury. Tans and Poortvliet (1983), also using the PVI in patients, state that the values of 10 ml and 13 ml are key values, with lower values indicating that active ICP reduction and improvement in compliance are required.

Marmarou's mathematical model developed an improved understanding not only of lumped intracranial compliance but also of the inter-relationships of the static and dynamic processes of formation, storage and absorption mechanisms of CSF. Clearly, the balance between formation and storage is critical and if the absorption of CSF is hindered, perhaps as a result of increased CSF outflow resistance, this will result, once the storage capacity of CSF becomes exhausted, in raised ICP. There is a clear relationship between CSF pressure and cerebral venous pressure and Davson (1967) has shown that, by withdrawing CSF at the estimated rate of CSF production (approximately

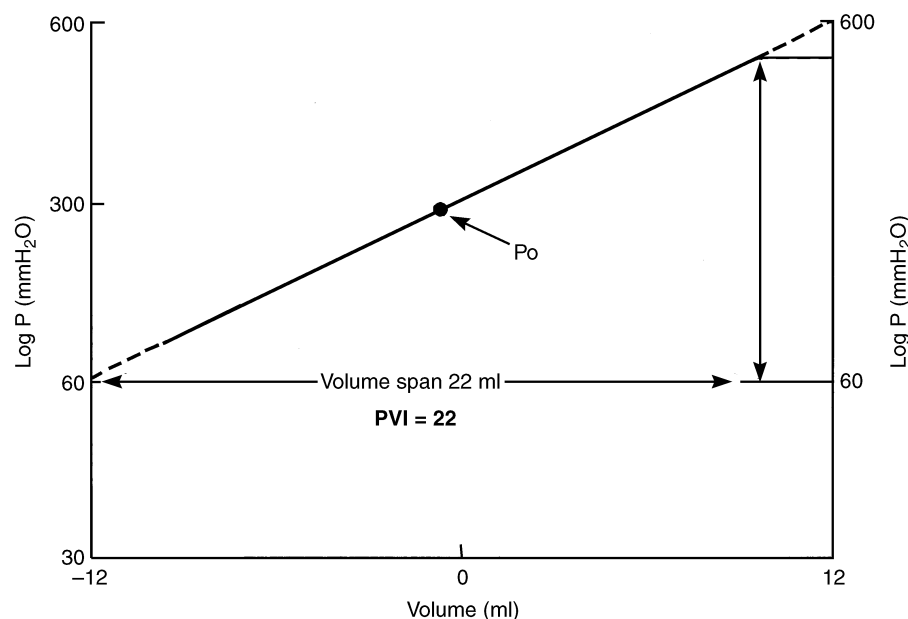


Figure 6.2 Log intracranial pressure (ICP) versus intracranial volume relationship defined by Marmarou (1973). The pressure volume index (PVI) is the notional volume (ml) which, when added to the craniospinal volume, causes a tenfold rise in ICP.

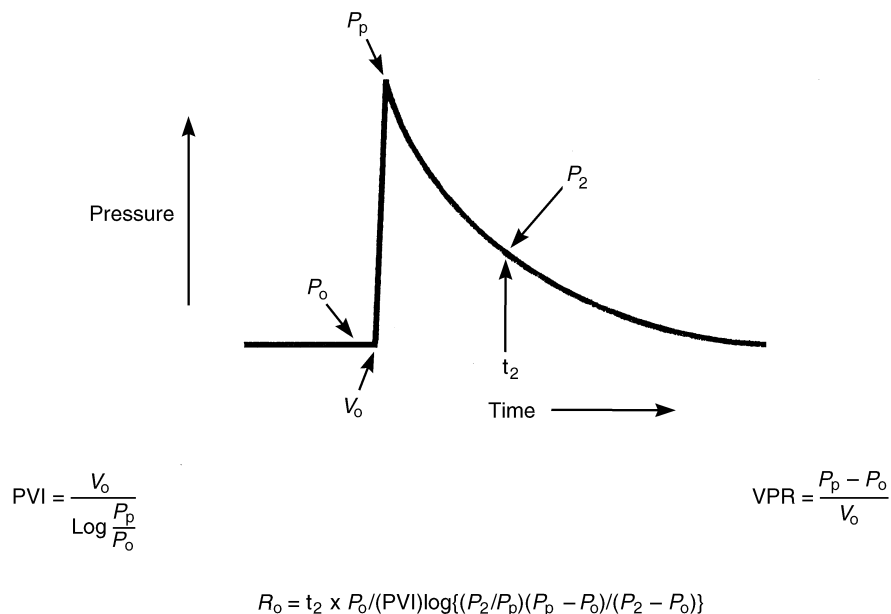


Figure 6.3 Formulae for deriving the pressure volume index (PVI), volume pressure response (VPR) and the CSF outflow resistance (R_0) where P_0 is the baseline CSF pressure, P_p is the peak pressure resulting from a bolus volume injection V_0 and P_2 refers to the pressure point on the return trajectory at time T_2 (usually selected at 2 min postinjection).

0.3 ml/min), it is possible to determine the baseline cerebral venous pressure. This value can then be substituted into the steady-state ICP equation:

$$\text{ICP} = \text{formation rate} \times \text{outflow resistance} + \text{venous pressure.}$$

Marmarou has extended Davson's work and his general solution for intracranial pressure allowed the derivation of an equation for CSF outflow resistance based on a bolus injection technique (Marmarou, 1973; Marmarou, Shulman and LaMorgese, 1975). Through a single volume injection (V_0) and noting the starting pressure (P_0), peak pressure resulting from the volume injection (P_p) and the pressure (P_2) on the return trajectory at a time (t_2 – usually 2 minutes), the outflow resistance (R_0) can be calculated (Figure 6.3). In head injury management, the usefulness of knowing CSF outflow resistance stems from the premise that increased CSF outflow resistance is one possible 'non-vascular' cause of raised ICP. *In general terms, causes of raised ICP can be categorized into 'vascular' and 'non-vascular' mechanisms. Vascular mechanisms would include active cerebral vasodilation due to stimuli such as increased CO_2 levels or decreased arterial inflow pressure (assuming intact pressure autoregulation) or passive distention of cerebral vessels in the absence of autoregulation or by venous outflow obstruction. Non-vascular mechanisms would include increases in brain bulk due to increased brain water content (edema) or to an increasing intracerebral, extradural or subdural mass. A further*

non-vascular mechanism would be an increase in CSF outflow resistance, possibly due to obstruction in the normal CSF pathway, which results in dilation of the channels proximal to the site of the obstruction.

The development of a simple bolus method for measurement of CSF outflow resistance has led to work validating the bolus method against both constant infusion and perfusion methods. Takizawa, Gabra-Sanders and Miller (1985) confirmed the earlier data of Sullivan *et al.* (1979), indicating that, under baseline conditions, there was a significant correlation between steady-state and dynamic measurements of CSF outflow resistance, but the slope of the regression line was less than unity so that the bolus method progressively underestimated CSF outflow resistance compared to the steady-state method. However, a separate set of measurements was obtained after the CSF system was loaded by infusion of artificial CSF so that the baseline feline PVI decreased from 0.72–0.56. This had no effect on the linear relationship between dynamic and steady-state measurements, but did produce a regression line with a much better fit to unity. Thus, under those clinically relevant conditions where volume buffering is likely to be decreased, the bolus method provides an adequate measure of CSF outflow resistance.

CSF outflow resistance measurement is used less often in head injury research but is generally accepted as valuable in the diagnosis of diseases associated with disturbances in the CSF dynamics. Thus, techniques for measuring CSF outflow resistance have

found widespread application in research into hydrocephalus (Katzmann and Hussey, 1970; Ekstedt, 1978; Borgesen and Gjerris, 1982; Tans and Poortvliet, 1984; Borgesen *et al.*, 1989; Maksymowicz *et al.*, 1993), the origin of 'B-waves' and as a means of timing shunt placement (Dirnagl *et al.*, 1989; Tans and Poortvliet, 1984; Tanaka and Nishimura, 1989; Goderski and Graff-Radford, 1993). Using these bolus techniques, Marmarou has extended their utility in head injury by demonstrating that, through measurement of the PVI and CSF outflow resistance, it is possible to calculate the percentage contribution of CSF and vascular factors to the elevation of ICP (Marmarou *et al.*, 1987).

This important study has shown that the CSF contribution to ICP in severely head-injured patients accounts for only about 30% of the ICP rise while the majority of ICP is attributable to vascular mechanisms. Recently, one of the basic assumptions underlying ICP dynamics tests has been called into question: that venous outflow pressure, as estimated by sagittal sinus pressure, remains constant. Marmarou *et al.* (1993), measuring jugular bulb pressure as an estimate of sagittal sinus pressure, showed that sagittal sinus pressure may be elevated in approximately 40% of severely head-injured patients. Also, in those patients with a significant correlation between jugular bulb pressure and intracranial pressure, there was a significantly higher percentage vascular contribution to ICP elevation. *This work shows that elevation of venous outflow pressure does contribute to ICP elevation and that assessment of CSF outflow resistance, PVI and jugular bulb pressure may, in selected patients, be useful to measure when targeting therapy for raised ICP.*

At about the same time that Marmarou introduced the PVI technique, Miller and co-workers (Miller and Garibi, 1972; Miller, Garibi and Pickard, 1973) defined a further measure of the craniospinal volume–pressure relationship, the volume pressure response (VPR). *The VPR, calculated from the intracranial pressure response resulting from a rapid bolus injection of saline into the CSF space, was a direct measure, not of compliance, but of its inverse: elastance.* The VPR technique was in several ways preferable to the PVI technique in that it was a simpler measure of craniospinal volume depletion, involving none of the assumptions about the monoexponential nature of the pressure *versus* volume relationship inherent in Marmarou's technique. Furthermore, the VPR increases in value as the patient's condition worsens, which makes it easier to understand clinically.

Miller pointed out that if there were only a single volume–pressure curve then no new information would be gained by measuring compliance or ela-

stance, and a knowledge of absolute ICP alone would suffice in determining the state of a patient's craniospinal volume decompensation. However, Miller and coworkers (Miller and Pickard, 1974; Miller, 1975; Miller, Leach and Pickard, 1975) have shown that *the shape of the volume–pressure relationship changes under a variety of conditions between patients and within patients at different times and under different circumstances.* In head-injured patients, the VPR correlated better to the degree of brain midline shift, as imaged on CT scan, than it did to absolute ICP alone. The VPR served as an indicator for surgical decompression, critical levels being between 3–5 mmHg/ml (Miller, Garibi and Pickard, 1973; Hase *et al.*, 1978).

Löfgren (1973; Löfgren, von Essen and Zwetnow, 1973; Löfgren and Zwetnow, 1973, 1976) extended the ICP range over which the volume–pressure relationship was studied, including a negative pressure range (relative to atmospheric pressure). In experimental studies in dogs using spinal block techniques, he showed *the volume–pressure curve to be the sum of two separate curves representing high compliance related to the spinal portion of the dural sac and a low compliance curve, at elevated ICP, related mostly to the cranial portion (Figure 6.4).* At the most elevated ICP, there was a sudden decrease in elastance as ICP approached diastolic pressure, possibly due to shifting of blood from the vascular bed when CBF ceased (Löfgren, von Essen and Zwetnow, 1973).

The importance of vascular factors as a determinant of lumped craniospinal compliance was demonstrated clearly by the work of Gray and Rosner (1987a, b), who showed that, when CBF autoregulation was intact with cerebral perfusion pressure (CPP) levels greater than 50 mmHg, there was a linear increase in PVI with increasing CPP. However, with CPP's below the autoregulatory range, CBF fell progressively followed this time by increases in the PVI again. This work demonstrates that *the PVI is a complex function of CPP, the direction of the CPP–PVI relationship being dependent on whether CPP is above or below the autoregulatory range for CBF (Figure 6.5).*

Not only is craniospinal compliance critically dependent on vascular factors but Anile, Portnoy and Branch (1987) have demonstrated that compliance is also time-dependent. They showed that the VPR calculated from slow, medium and rapid bolus injections yields different values. They conclude that lumped craniospinal compliance can be divided into two components based on the rate of injection of the volume bolus: physical compliance and physiological compliance. *Physical compliance is a measure of such factors as expansion of spinal dura matter and of any minute amount of brain compression and skull expansion that may occur (Heifetz and Weiss, 1981).*

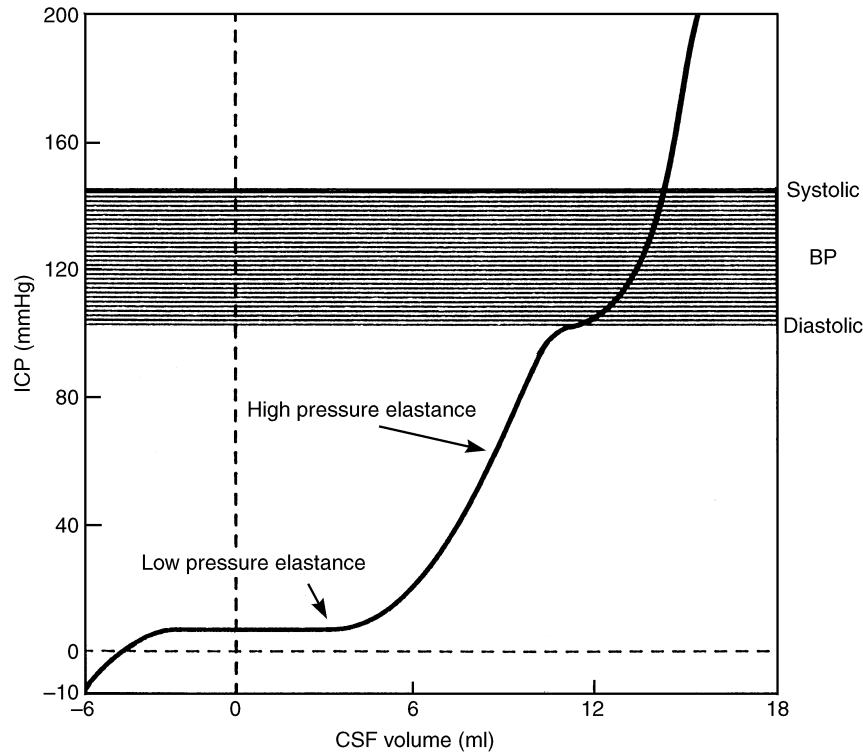


Figure 6.4 Extended craniospinal volume–pressure relationship defined by Löfgren (1973), demonstrating ‘low’ and ‘high’ elastance regions.

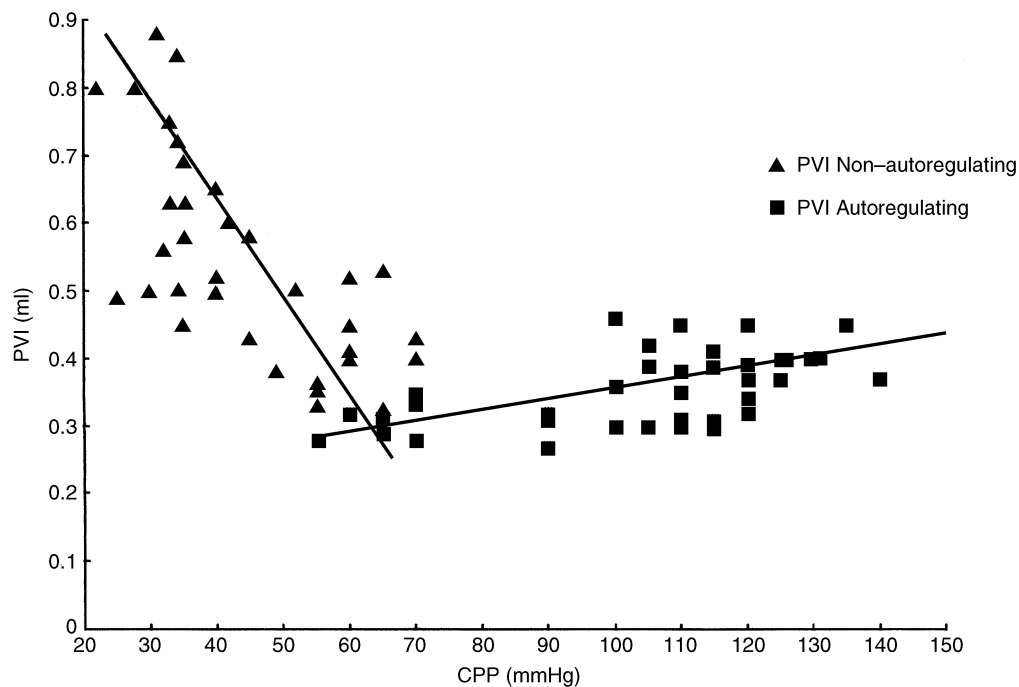


Figure 6.5 Plot showing the pressure–volume index (PVI), as a measure of compliance, *versus* cerebral perfusion pressure (CPP), both within (squares) and beyond (triangles) an ‘autoregulating range’ of CPP. Autoregulation was defined as intact if cerebral blood flow measurements taken at the time of the PVI measurements were within 15% of baseline values. Note that the lines of best fit through the PVI/CPP relationships have slopes of different direction depending on whether the CPP range is within or beyond the autoregulating range. (Source: adapted from Gray and Rosner, 1987.)

Physiological compliance of the intracranial system is related to cerebrovascular alterations, particularly venous outflow resistance (Chopp and Portnoy, 1983).

These data show that, to understand craniospinal pressure–volume relationships, the dynamic and the viscoelastic properties of CSF, nervous tissue and vascular factors must all be considered. Zee and Shapiro (1989), using a gas-bearing electrodynamicometer and a linear variable displacement transducer, measured the relationship between brain compression force and displacement to study the viscoelastic properties of the brain. They demonstrated that dogs, made hydrocephalic with intracisternal injection of kaolin, developed brains that became less stiff (more compliant) and more viscous than normal brain. They propose that this weakening of brain tissue may account for the increase in brain compliance associated with hydrocephalus, although the time course of these changes is still unknown.

Walsh and Schettini (1989) have shown that brain tissue elasticity bears no relation to lumped craniospinal elastance as measured by the VPR. The brain elastic response was measured extradurally with a coplanar transducer recording the brain displacement simultaneously with the pressure required to cause that brain displacement. The resulting pressure *versus* brain displacement relationship is similar to the pressure *versus* injection volume relationship previously described. The tangent of this brain elastic response curve is a parameter G_0 which is a measure of brain tissue elasticity. They have shown in ten dogs, in an extradural balloon-inflation model of raised ICP, that the VPR increases with increasing ICP but G_0 remains unchanged. Upon cardiac arrest, however, the VPR decreases and G_0 increases. They propose that G_0 increases as a result of an ion shift from the extracellular to the intracellular compartment, leading to increased intracellular water and hence increased cellular tension (Van Harreveld and Ochs, 1956).

From this work it is clear that a knowledge of a patient's craniospinal volume–pressure relationship is an adjunct to ICP measurement for predicting states of raised ICP. However, the use of the PVI or VPR methods is not without disadvantages. With these techniques there is an increased risk of infection, usually due to *Staphylococcus epidermidis*, with reported infection rates ranging from 0.5% up to 9% (Lundberg, 1960; Wyler and Kely, 1972; Troupp and McDowell, 1976). Infection is a particular complication of ventriculostomy and relates to the duration of monitoring. Narayan *et al.* (1982) found an 8.5% incidence of ventriculostomy-related infection in patients monitored for over 5 days but no similar infections in patients monitored for 3 days or less. This relationship of duration of monitoring to risk of infection has not been confirmed by others, and the

rate of access to the CSF system to obtain samples or to recalibrate may be important. Other disadvantages include a risk of provoking secondary pressure rises with rapid volume injection through activation of secondary vasodilation (Avezaat and Van Eijndhoven, 1984; Langfitt *et al.*, 1974). Furthermore, variability between measurements is high as it is difficult to manually inject consistent volumes of fluid rapidly at a constant rate of injection. As a result an average of repeated measures is usually required.

As a consequence of these limitations the PVI or VPR tests are not routinely used in neurosurgical practice. In an effort to find a less invasive means to obtain this data Avezaat and Van Eijndhoven (1979; Avezaat, Van Eijndhoven and Wyper, 1984) systematically studied the ICP waveform pulse amplitude (ICP_{plse}) as a measure of craniospinal elastance. The rationale behind this concept is that *with each heartbeat there is a pulsatile increase in cerebral blood volume, the equivalent of a small intracranial volume injection, and the ICP_{plse} is the intracranial pressure response to that volume increment and should therefore be directly related to the craniospinal elastance (dP/dV)*. That is, as craniospinal elastance increases (compliance decreases) the ICP_{plse} should increase, provided that the volume increment remain constant. The observation that as ICP increases so does the amplitude of the intracranial pressure pulsations is not a new one, having been first described in 1866 by Leyden.

Avezaat and Van Eijndhoven first extended the mathematical description of the exponential craniospinal volume–pressure relationship by introducing a constant term P_0 into the pressure–volume equation (Figure 6.6). Primarily for mathematical convenience this term shifts the volume–pressure curve as a whole up or down its axis, which allows correction for pressure transducer reference position and postural changes. Mathematically, P_0 is the pressure at zero elastance (see the equation in Figure 6.6) and must therefore have physiological significance as a determinant of the normal intracranial equilibrium pressure (P_{eq}). Löfgren and Zwetnow (1973) showed that alterations in CVP can shift the pressure–volume curve up or down its axis, which would suggest CVP may be a factor determining P_0 .

Avezaat and Van Eijndhoven described the mathematical relationship between ICP_{plse} and ICP by substituting the ICP_{plse} for the elastance (dP/dV) and pulsatile blood volume for the volume injection. This relationship was verified in both clinical and experimental studies. They found that the ICP_{plse} increased linearly with ICP up to a pressure of 60 mmHg, whereupon a breakpoint occurred (Figure 6.7). Above 60 mmHg the ICP_{plse} increased more rapidly with rising ICP. They argue that the breakpoint is a marker for loss of CBF autoregulation, postulating that onset of

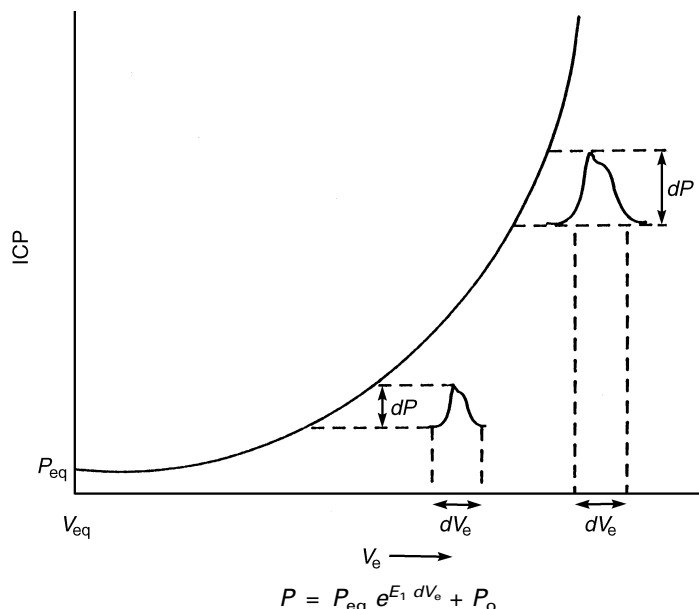


Figure 6.6 Craniospinal volume–pressure relationship demonstrating that for the same increase in craniospinal volume (dV_e) the ICP pulse amplitude (dP) increases when total craniospinal volume (V_e) increases. This is due to the exponential nature of the curve, which is described mathematically by the equation. $P = ICP$; P_{eq} = equilibrium ICP; E_1 = elastic coefficient; V_e = elastic volume (addition to total volume); P_0 = constant term.

vasomotor paralysis causes a decreased arteriolar inflow resistance, which results in an increased phase shift between the inflow and outflow pulsatile blood volume. This translates to an overall increased intracranial pulsatile blood volume and will tend to increase the slope of the ICP_{plse} versus ICP relationship.

It is assumed that the pulsatile blood volume (dV), the input function to the elastance calculation (dP/dV), is unchanging. This is a tenuous assumption in

severely injured patients, some of whom may have compromised or fluctuating cardiovascular function. As a consequence of the dependence of the ICP_{plse} versus ICP relationship on the pulsatile blood volume, the clinical utility of this technique as a measure of lumped craniospinal elastance is limited unless a measure of the pulsatile blood volume can be monitored simultaneously and controlled for in patients. Despite this limitation, analysis of the ICP pulse

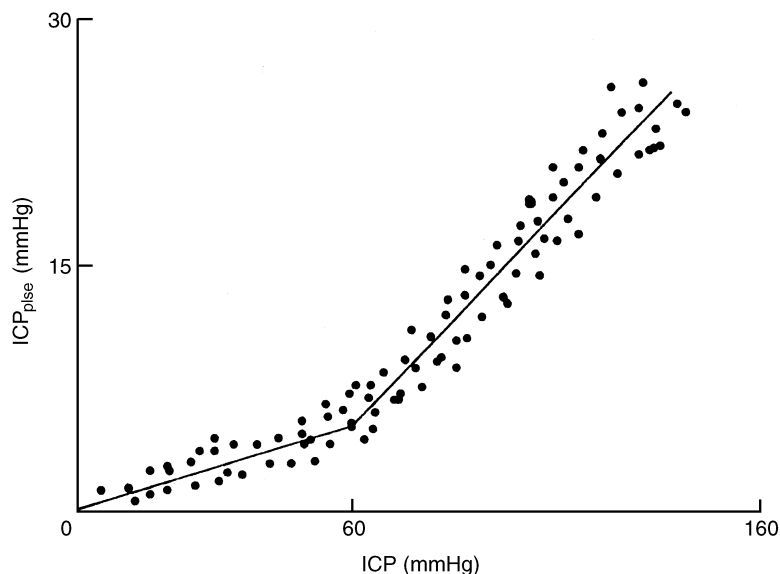


Figure 6.7 ICP pulse amplitude (ICP_{plse}) versus intracranial pressure relationship defined by Avezaat and Van Eijndhoven (1979), demonstrating a direct linear dependence of ICP_{plse} on mean ICP. A breakpoint occurs at an ICP of approximately 60 mmHg whereupon the slope of the relationship increases.

amplitude is still widely studied clinically and may, in the future, prove useful as an estimate of cerebrovascular autoregulatory reserve (Laniewski, Czosnyka and Maksymowicz, 1993).

Portnoy and Chopp recognized the importance of measurement of the input function in an analysis of the ICP_{plse} and were the first to apply a systems analysis approach to the ICP waveform (Chopp and Portnoy, 1980). *Systems analysis is a technique whereby an attempt is made to define the physical characteristics of a system using only the system input and output signals (Marmareliz and Marmareliz, 1987). Portnoy and Chopp's method assumes that the BP waveform is the chief input signal to the cerebrovascular system and the ICP waveform is the output response to that stimulus.* Both BP and ICP waveforms are converted into the frequency domain by Fourier analysis, and the resulting frequency spectra are used in the calculation of the system transfer function (Figure 6.8). The system transfer function consists of amplitude and phase components. The amplitude transfer function is a measure of how much pressure is transmitted through the cerebrovascular bed at a given frequency. The phase transfer function is a measure of how much a pressure signal is phase-shifted as it is transmitted through the cerebrovascular bed at a given frequency.

Using these methods, Portnoy and Chopp (1981) found, in an experimental model of raised ICP in cats, that arterial hypercarbia and hypoxia produced an increase in ICP_{plse} and an increase mainly in the fundamental of the amplitude transfer function. The changes induced were greater than those caused by intraventricular infusion of saline to the same ICP level. The VPR was less during hypercapnia than during intraventricular infusion at the same ICP level, which suggests that the increase in ICP_{plse} is related more to arteriolar vasodilation than to steepening of the craniospinal volume–pressure relationship.

Extending their model by including analysis of the sagittal sinus pressure (SSP) waveform in dogs, Portnoy *et al.* (1982) found that the ICP waveform and SSP waveform were almost identical, indicating that the ICP_{plse} is derived from the cerebral venous bed. With the animals breathing pure oxygen it was observed that an attenuation of the amplitude transfer function fundamental occurred in the transmission of the arterial pulse through to the CSF space under conditions of low ICP ($ICP < 7$ mmHg). They attributed this attenuation to functional autoregulatory tone of the precapillary cerebral resistance vessels, and further demonstrated that a flat amplitude transfer function (equal transmission of all harmonics) can be experimentally induced by intraventricular infusion

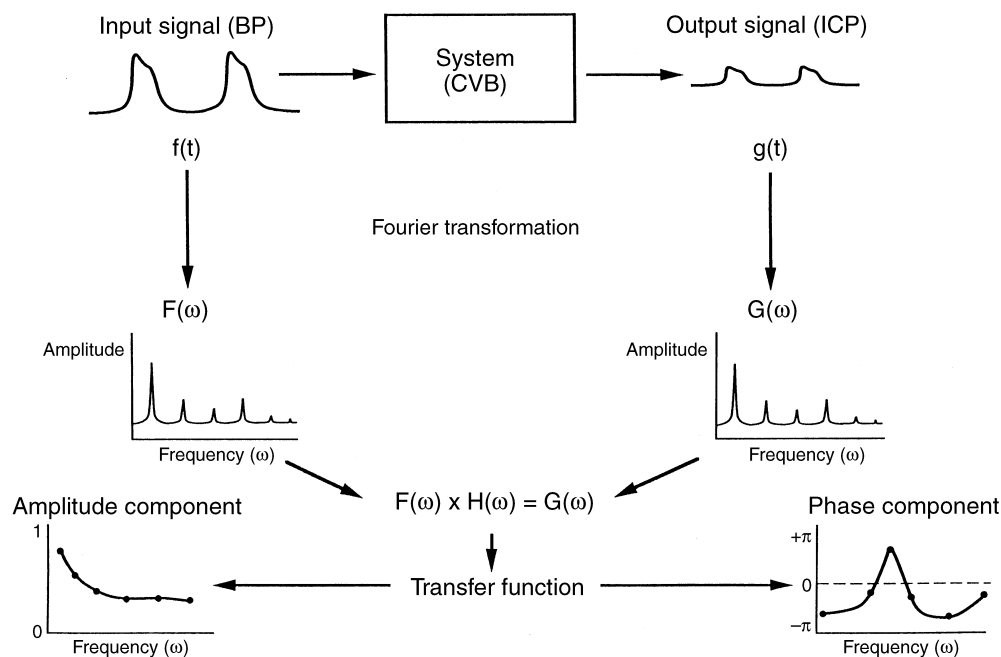


Figure 6.8 Systems analysis. The input blood pressure ($f(t)$) and output intracranial ($g(t)$) waveforms recorded from locations across the cerebrovascular bed (CVB) can be described by spectral analysis in terms of their harmonic components ($F(\omega)$ and $G(\omega)$). Spectral analysis of the BP and ICP signals resolved each waveform as a series of sine waves consisting of a fundamental component and five harmonics of the fundamental. The transfer function ($H(\omega)$) defines how the input signal is transformed into the output signal and consists of amplitude and a phase components. The amplitude curve describes how much pressure is transmitted through the CVB at each harmonic frequency. The phase curve describes how much each pressure sine wave is shifted in its cycle as it is transmitted through the CVB.

of mock CSF or arterial hypercarbia. They propose that the conversion from an attenuated low frequency transmission to a flat amplitude transfer function is evidence for reduced arteriolar vasomotor tone.

Applying these techniques to hydrocephalic dogs, Portnoy, Branch and Chopp (1985) found that, when ICP was less than 9 mmHg, there was an attenuated low-frequency transmission from BP to ICP; however, when ICP was greater than 12 mmHg a flat amplitude transfer function was present. These findings in hydrocephalic dogs were identical to non-hydrocephalic controls, and they concluded that pressure transmission from BP to ICP in hydrocephalic dogs was determined by the cerebrovascular bed and not by the hydrocephalic process.

Branch, Chopp and Portnoy (1989), recording the pressure waveform from a small cortical vein, provided further evidence that the ICP waveform was derived from the cerebral venous bed by demonstrating that the ICP and cortical venous amplitude spectra were identical across a variety of experimental conditions.

Using similar techniques to Portnoy and Chopp, Takizawa, Gabra-Sanders and Miller (1987) have shown that the first four harmonics of the ICP waveform and the amplitude transfer function all show a positive correlation to raised ICP and an inverse correlation to CPP. A distortion factor 'k' was used to show that, as ICP increased towards 50 mmHg the ICP waveform became more like a sine wave, changing less as ICP continued to increase. Takizawa, Gabra-Sanders and Miller (1986b) also found that cerebrovascular pressure transmission increased with saline infusion and arterial hypercarbia equally when ICP was recorded either in the lateral ventricle or in the cisterna magna, but transmission was attenuated in the lumbar space. This attenuation in the lumbar space was decreased by saline loading of the cranio-spinal axis. They propose that the spinal sac functions as a low-pass filter to the conduction of the ICP_{plse}.

Also using a systems analysis approach to studying cerebrovascular pressure transmission, but using different methods, Kasuga *et al.* (1987) have demonstrated resonance within the intracranial cavity in dogs. They randomized pressure pulse transmission into the cranial cavity through the control of an implanted cardiac pacemaker. Using the carotid pulse waveform as an input function and the extradural pressure waveform as the output function, they calculated the transfer function from the autocorrelation of the input function and the cross-correlation of the input and output functions by means of a least squares method. They showed that the amplitude transfer function decreased between the frequencies of 1 and 7 Hz, then suddenly increased to form a marked peak at about 10–15 Hz, whereupon the phase transfer

function also changed from positive to negative. This showed that the lower frequencies of the pulse wave were suppressed during transmission through the intracranial cavity and that resonance was present under normal intracranial conditions. Kasuga, Nagai and Hasegawa (1989) subsequently showed that, with both extradural balloon inflation and intraventricular infusion models of raised ICP in dogs, the resonant frequency increased above the control value. Associated with this increase in resonant frequency, there was an increased transfer of the low frequency components. However, with arterial hypercarbia, ICP increased but with no significant change in the resonant frequency, although low-frequency pressure transmission increased in a similar fashion to both groups.

Bray and Robertson (Bray *et al.*, 1986), also using Fourier analysis of the ICP waveform in patients, identified two main frequency bands in the ICP waveform power spectrum. The centroid (power-weighted average frequency) of the low frequency band (0.2–2.6 Hz) they correlated to cerebral blood flow using the nitrous oxide method, while the high-frequency band centroid (4–15 Hz) they found inversely correlated to the PVI as a measure of craniospinal compliance. Further clinical experience (Robertson *et al.*, 1989) with the high-frequency centroid showed that the percentage of time spent with a high-frequency centroid greater than 9 Hz bore no relation to ICP but that the centroid frequency correlated exponentially to increased mortality. Case reports showed that the high-frequency centroid was a better measure of the clinical state of the patient than was the absolute ICP alone. However, subsequent work shows that the high-frequency centroid is also affected by heart rate thus diminishing its predictive reliability (Contant *et al.*, 1993).

Adapting the systems analysis method of Portnoy and Chopp to a clinical study of cerebrovascular pressure transmission, Piper *et al.* (1990a), in an observational study of 1500 pressure records in 30 severely head-injured patients, identified *four patterns of amplitude transfer function. Both forms that showed an elevated fundamental pressure transmission from BP to ICP were associated with raised ICP, whereas the remaining forms with a normal fundamental amplitude transfer function were associated with ICP less than 15 mmHg.* Following on from this work a further explanatory experimental study was performed in cats, demonstrating that the fundamental amplitude transfer function can be increased by active arteriolar vasodilation, by loss of autoregulatory vascular tone, or through reduced cerebrovascular transmural pressure (Piper *et al.*, 1993). It may be possible to distinguish these mechanisms, working from the observed phase shift between the

fundamental of the BP and ICP waveform. In this experimental model, active arteriolar vasodilation was followed by an increasingly negative phase shift and decreased transmural pressure resulted in no overall phase shift whereas impaired autoregulation showed that an increased fundamental amplitude was accompanied by a positive phase shift. Further studies are needed that correlate these ICP waveform measures with CBF and pressure autoregulation in head-injured patients.

Another area of research showing promise as a means of studying the effect of intracranial hypertension on craniospinal compliance and autoregulatory reserve concerns the continuous measure of transcranial middle cerebral artery (MCA) flow velocity and its correlation with CPP. Chan *et al.* (1993) demonstrated that, in continuously monitored head-injured patients, *the MCA Doppler pulsatility index (PI; systolic–diastolic/mean flow velocity), when plotted against CPP, showed a breakpoint at 70 mmHg below which the PI increases. Simultaneous measurement of jugular venous oxygen saturation in the same patients demonstrated a fall in jugular venous saturation towards ischemic levels from the same CPP breakpoint. This data would indicate that below a CPP threshold of 70 mmHg autoregulation in these patients was becoming exhausted (Chapter 14).* This information is useful as it provides a means of determining the optimal CPP threshold for treating raised ICP at any time during the management of head-injured patients. If there was only one ‘critical

CPP threshold’ it would be a simple matter to treat if CPP fell below this threshold. However, there is now increasing evidence, from both clinical and experimental studies, that as a result of the varying severity of head injury and the development of the injury process with time, the critical CPP threshold changes both between patients and within patients on different days (Price *et al.*, 1994; Wong *et al.*, 1995; Lewis *et al.*, 1995). *The development of analysis methods for detecting changes in CPP breakpoint may have a significant impact on the future management of cerebral perfusion.*

A similar relationship between CPP and exhaustion of autoregulation may also be identified through analysis of the ICP waveform (Figure 6.9). Although this relationship is currently under study in head-injured patients, it confirms the earlier experimental study in cats of Takizawa, Gabra-Sanders and Miller (1987), who demonstrated that the fundamental amplitude transfer function showed a positive correlation to raised ICP and an inverse correlation to CPP, with the latter demonstrating a breakpoint phenomenon as CPP exceeded 60 mmHg.

Much of the work just described shows promise in elucidating the status of cerebral autoregulation in head-injured patients, but we are still no closer to improving upon the methods developed by Marmarou and Miller for assessment of the craniospinal volume–pressure status. However, some of the limitations of these manual volume–pressure techniques are now being overcome as a result of innovative applica-

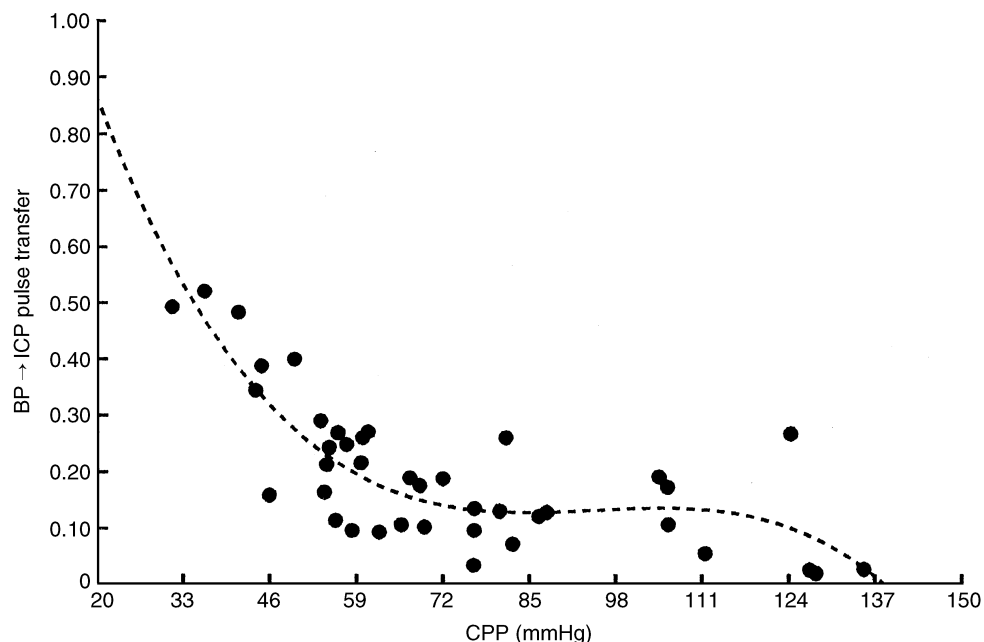


Figure 6.9 Plot of the ICP-waveform-derived parameter (ICP pulse to BP pulse ratio) *versus* cerebral perfusion pressure (CPP). At a CPP of less than 70 mmHg, a breakpoint occurs where there is an increasing transfer of the BP pulse through to the CSF.

tion of computer technology. For example, Smielewski *et al.* (1993) reported a new method of measuring craniospinal compliance and CSF outflow resistance in hydrocephalic patients, based on controlled CSF drainage. This system uses an electromagnetically driven clamp, which opens or closes the outlet of the lumbar drain under computer control, permitting on-line controlled drainage of CSF, measurement of CSF pressure and volume. This automated drainage method does not raise ICP and so overcomes the risk of provoking uncontrolled rises in ICP associated with the continuous infusion or bolus techniques. Similarly, Piper *et al.* (1990b) reported on an automated method for measuring craniospinal compliance based on an electronic square wave pressure generator triggered under computer control and able to produce small (0.05 ml) volume injection/withdrawal sequences into the CSF space. The compliance is calculated with this method from the amplitude of the intracranial pressure response to this small volume increase. The resulting pressure response itself is small (1–2 mmHg) and is isolated from background noise using computer-controlled signal averaging. Work is under way

developing a practical clinical device based on this technique for measuring craniospinal compliance in patients at risk of raised ICP.

Also as a result of improvements in both hardware and software computer technology, it is becoming more practical to develop increasingly complex mathematical models of the craniospinal system. Some investigators have modeled the craniospinal and cerebrovascular systems as second- or higher-order systems containing a series of distributed resistive, inductive and capacitive components (Takemae *et al.*, 1987; Hoffmann, 1987; Sorek, Bear and Karni, 1988; Ursino, 1988). More recently, finite element analysis has been applied to model the viscoelastic properties of the brain (Nagashima, Shirakumi and Rapoport, 1990; Hamano *et al.*, 1993). Such models are becoming increasingly useful as methods for the controlled testing of hypotheses and simulation of physiological conditions that would otherwise be difficult to reproduce in animal models. For example, Czosnyka *et al.* (1993) developed a mathematical model of the cerebrovascular bed and craniospinal compartment (Figure 6.10). The electrical equivalent circuit of this model

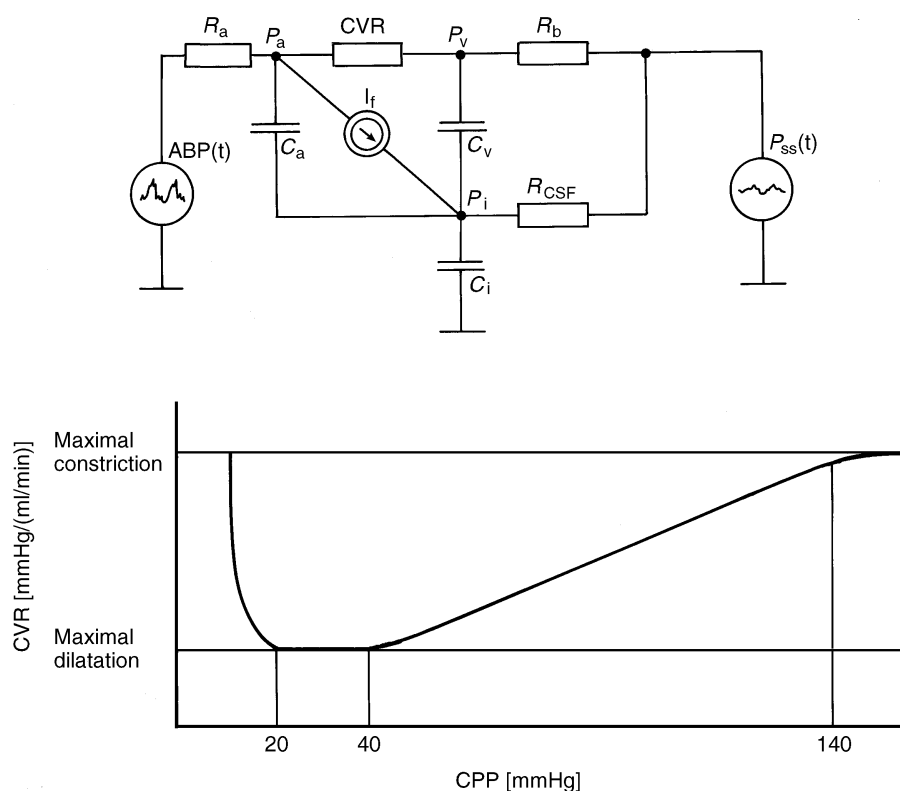


Figure 6.10 Electrical equivalent circuit of a cerebral blood flow (CBF) and CSF circulation model developed by Czosnyka *et al.* (1993). The upper figure defines the model parameters and the lower figure shows the autoregulatory relationship between vascular resistance (CVR) and CPP. ABP = arterial blood pressure; P_a = arterial pressure in basal cerebral arteries; P_v = cerebral venous pressure; P_i = intracranial pressure; P_{ss} = sagittal sinus pressure; C_a = compliance of arterial bed; C_v = compliance of venous bed; C_i = compliance of CSF lumbar compartment; I_f = CSF formation rate; R_{CSF} = CSF reabsorption; R_b = resistance of bridging veins; R_a = resistance of basal arteries; CVR = main cerebrovascular resistance.

comprises arterial and venous resistances, capacitances (or compliance), CSF formation rate, a non-linear craniospinal compliance, CSF outflow resistance and arterial and venous pressure sources. What is particularly useful in this model is the non-linear arterial resistance characteristic (Figure 6.10), which allows representation of the autoregulatory process to changes both in cerebral perfusion pressure and arterial CO₂. Using this model it was possible analytically to define the CPP-dependent ICP pulse amplitude and transcranial Doppler flow-velocity relationship. This confirmed the earlier experimental and clinical data of Avezaat, Van Eindhoven and Wyper (1979), Takizawa, Gabra-Sanders and Miller (1987), Czosnyka *et al.* (1990) and Chan *et al.* (1992).

In conclusion, current research using multimodality monitoring and applied computer technology is a most promising approach to the study of raised ICP and may prove to be a powerful aid in the investigation of cerebrovascular pathophysiology and craniospinal volume-pressure relationships.

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